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VISCERAL LESIONS ASSOCIATED WITH CHRONIC INFECTIOUS (RHEUMATOID) ARTHRITIS

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Patients suffering with rheumatoid arthritis frequently present much evidence that the disease is not confined to the joints. For this reason many physicians have felt that rheumatoid arthritis is a generalized disease of which the arthritis is but a single manifestation. From a clinical standpoint it is easy to detect profound disturbances of the functions of a number of organs among such patients but curiously, only fragmentary data concerning the visceral pathologic changes of this disease have been reported. Consequently, little is known as to the morphologic changes which may be at the basis of the visceral or systemic manifestations of rheumatoid arthritis.

In 1890 Garrod [1] wrote that such visceral lesions as may be found at necropsy in patients who have suffered from rheumatoid arthritis are, with a few possible exceptions, ascribable to intercurrent diseases and not to the disease of the joints. This view has been accepted almost without question to the present time and the same view was reflected only recently in a publication by a well known modern authority on arthritis (Copeman [2]), who stated that the viscera are "rarely" affected in rheumatoid arthritis and that the disease therefore rarely shortens life. Kuhns [3] and Kuhns and Joplin [4] have reported recently on 76 cases of "atrophic arthritis," in about half of which, according to a personal communication, necropsy was performed. They reported that in many of their cases arteriosclerosis had developed rapidly, and they noted that an unstated number of their patients had resulting myocardial

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1. Garrod, A. E.: A Treatise on Rheumatism and Rheumatoid Arthritis, Philadelphia, P. Blakiston, Son & Co., 1890, pp. 261-263.

2. Copeman, W. S. C.: J. Roy. Inst. Pub. Health & Hyg. **1**:623, 1938.

3. Kuhns, J. G.: Personal communication to the authors.

4. Kuhns, J. G., and Joplin, R. J.: New England J. Med. **215**:268, 1936.

or renal lesions. Death was said to have been caused by pneumonia in 18, by myocarditis in 13, by nephritis in 11 and by postoperative complications in 6. In 28 instances, the causes of death were "miscellaneous." No more intimate description of the visceral lesions was reported in their paper.

Still's disease, which is considered to be a form of rheumatoid arthritis present in children, was described recently by Portis [5] as being associated with distinct, though not pathognomonic, visceral lesions. The findings included hyperplastic lymph nodes. Histologic examination revealed proliferation of reticulum cells in the lymph nodes, hyperplasia of the spleen, and passive congestion and fatty degeneration of the liver.

With the exception of these studies, no extensive reports of necropsies on the visceral aspects of rheumatoid arthritis have been made in recent years. We undertook the present study primarily with a view to determining the nature of the anatomic changes which occur in the viscera of these patients. We also hoped that we might be able to throw some light on the present obscure causation and genesis of this disease.

MATERIAL AND METHODS

We included in our study the necropsies in all cases of rheumatoid arthritis. We found that a total of 30 cases had accumulated to this time. These 30 cases include 25 which formed the basis of a previous investigation on cardiac lesions of patients who had had rheumatoid arthritis, and 5 additional cases in which necropsy had been carried out since that paper was published. Our series was chosen so that it would include every instance of rheumatoid arthritis in the necropsy material of the Mayo Clinic. Our only requirement for inclusion in this study was that acceptable clinical criteria for the diagnosis of rheumatoid arthritis must have been fulfilled and evidence of the presence of these features must have appeared in the records. Our criteria were outlined in previous papers and are not repeated here. In each case an internist particularly interested in arthritis and the rheumatic diseases had passed on the diagnosis of rheumatoid arthritis. We found that only 2 patients recalled an illness which might have been rheumatic fever.

The patients included 17 men and 13 women. The mean age of these patients at the time of death was 37.6 years. The youngest patient was 9 years and the oldest 81 years of age. Only 5 patients were 60 years of age or more, and 18 were less than 50 years of age. Eleven of the patients were less than 40 years of age.

The data used for this study were obtained by first abstracting carefully the available clinical records of these patients. Subsequently we made gross examinations of all organs and made appropriate sections for histologic examinations from all structures which presented an abnormal gross appearance. Routinely also sections were taken from the heart and its valves, the adrenal glands, the kidneys, the lungs, the spleen, the liver and the pancreas even though these organs appeared normal at the time of the gross examinations.

The sections were stained routinely with hematoxylin and eosin. Van Gieson, Mallory-Heidenhain and Gram stains and silver impregnation methods were employed when indicated.

5. Portis, R. B.: Am. J. Dis. Child. **55**:1000, 1938.

The causes of death in the cases studied are listed in table 1. It is necessary to point out, however, that necropsy frequently revealed serious lesions in more than one vital organ, so that an unequivocal decision as to the principal cause of the patient's death has not always been possible.

OBSERVATIONS

Cardiac Lesions.—In a recent paper [6] we published details of the character of the lesions which we encountered in the hearts of 25 of the patients who constituted the present series. For the present we wish merely to summarize the findings in the hearts of the entire group.

In 16 (53 per cent) of the 30 patients we found rheumatic heart disease, and in 2 further patients we found lesions which may have been rheumatic in origin. The lesions of the 2 latter included calcific aortic stenosis and chronic pericarditis.

TABLE 1.—*Cause of Death in Thirty Cases of Rheumatoid Arthritis*

Cause of Death	Cases
Cardiac disease (9 cases)	
Rheumatic cardiac disease	7
Nonrheumatic cardiac disease	2
Renal disease (3 cases)	
Acute pyelonephritis with oliguria	2
Renal amyloidosis	1
Pulmonary disease (11 cases)	
Chronic bronchiectasis with pulmonary suppuration	2
Pulmonary embolism	3
Bronchopneumonia	3
Pulmonary fat embolism	2
Postoperative massive collapse	1
Intestinal disease (2 cases)	
Chronic diarrhea of undetermined origin	2
Miscellaneous causes (5 cases)	
Cinchophen hepatitis	1
Violent accidental death	1
Carcinoma of prostate with metastasis	1
Sudden unexplained death	1
Cause of death unknown	1
Total	30

In these 2 instances, however, the rheumatic nature of the heart disease was not certain. It was our opinion that 7 of the 16 patients with rheumatic heart disease had met death as a direct consequence of that disease. In 2 others rheumatic heart disease was a contributory cause of death.

Two of our patients died as a result of nonrheumatic forms of heart disease: one of coronary arterial occlusion and the other of severe myocardial degeneration of an undetermined cause.

In 6 patients nonrheumatic cardiac lesions were present, but these were minor in severity and were not considered to have contributed significantly to the cause of death. These lesions included (1) coronary sclerosis with chronic myocardial infarction, (2) hypertrophy of the heart resulting from hypertension, (3) hydropericardium, (4) nonspecific subacute pericarditis, (5) chronic obliterative pericarditis and (6) calcific aortic stenosis.

The number of patients in this series who gave a history of rheumatic fever was small; only 2 recalled an illness the description of which fitted that condi-

6. Baggenstoss, A. H., and Rosenberg, E. F.: Arch. Int. Med. **67**:241, 1941.

tion. This low number with a history of rheumatic fever is in striking contrast to the large number, 16, in whom we found clear evidence of rheumatic heart disease at necropsy.

Another notable observation of our study is the fact that clinicians had been able to discover clear evidence of rheumatic heart disease in only 1 of the 16 patients in whom that type of heart disease was present as proved by necropsy. This discrepancy is entirely unexplained as yet.

From a clinical standpoint it has long been known that the incidence of signs of rheumatic heart disease among patients suffering from rheumatoid arthritis is low. After encountering so large an incidence of rheumatic heart disease in the patients of this series, we restudied a number of patients suffering from rheumatoid arthritis in our wards to determine whether we had been overlooking minor signs of rheumatic heart disease. The result served only to confirm our previous clinical impressions, for we did not find a single instance of detectable

TABLE 2.—*Postmortem Observations on the Lungs in Thirty Cases of Rheumatoid Arthritis*

	Cases
Fibrous adhesions between parietal and visceral pleura (22 cases)	
Associated with pericardial adhesions	10
Associated with healed tuberculosis of lungs and hilar nodes	7
Associated with healed tuberculosis and hilar nodes only	4
Associated with chronic active tuberculosis of lungs	3
Bronchopneumonia (9 cases)	
Responsible for death	3
Terminal	6
With empyema	2
With pulmonary abscess	1
With organization	2
Bronchiectasis (3 cases)	
Mild	1
Severe (responsible for death)	2
Pulmonary embolism (4 cases)	
Fatal	3
Nonfatal	1
Pulmonary fat embolism	2
Emphysema	3
Bronchitis	1

rheumatic heart disease in a service of 15 persons suffering from rheumatoid arthritis.

Thus our findings in the hearts of patients in this series raise questions which cannot be answered satisfactorily at the present time: the question whether rheumatoid arthritis is responsible for a form of heart disease indistinguishable from rheumatic heart disease, and the question whether rheumatoid arthritis and rheumatic fever are related.

Pulmonary Lesions.—The notable pulmonary lesions encountered among these patients are outlined in table 2. Although we searched with care, we failed to find pulmonary lesions which might in any way be considered specific for rheumatoid arthritis. We likewise did not observe any condition which might be labeled rheumatic pneumonia despite the high incidence of rheumatic heart disease among these patients.

Fibrous adhesions, indicating episodes of pleurisy with healing, were noted in 22 cases. Since pleural adhesions are a common manifestation of tuberculosis, the possibility that these adhesions were the result of tuberculosis was considered. In a careful search for evidence of pulmonary tuberculosis, healed or chronic

tuberculous lesions were found elsewhere in the lungs in only 14 of the 22 cases in which there was healed pleuritis. We cannot be certain as to the relation of these evidences of healed pleuritis to rheumatoid arthritis, but we must assume that the inflammatory process of rheumatoid arthritis may manifest itself in the pleura as well as in the serous membranes of joints.

The presence of bronchopneumonia in 9 of the patients does not appear to be an unusually high incidence for a series of necropsies. It is noteworthy, however, that fatal bronchopneumonia was precipitated three times by various therapeutic measures directed against the arthritis, including typhoid vaccine shock therapy, tonsillectomy and lumbar sympathectomy.

TABLE 3.—*Postmortem Observations on the Liver in Thirty Cases of Rheumatoid Arthritis*

	Cases
Mean weight (23 cases only) 1,634.6 Gm.	
Heaviest (2,765 Gm.)	
Lightest (1,046 Gm.)	
Weighing more than 1,800 Gm.	8
Weighing more than 2,000 Gm.	4
Weighing less than 1,600 Gm.	10
Weighing less than 1,400 Gm.	8
Weighing less than 1,200 Gm.	4
Chronic passive congestion with atrophy of cells about central veins (18 cases)	
Grade 1*	8
Grade 2	9
Grade 3	1
Central necrosis (4 cases)	
Cause of death; rheumatic heart disease	2
Cause of death; pulmonary infections	2
Fatty change (7 cases)	
Grade 1*	2
Grade 2	4
Grade 3	1
Amyloid deposits	1
Subacute yellow atrophy (cinchophen hepatitis)	1
Healed miliary tuberculosis	1
Serous hepatitis (Rössle and Eppinger [6])	9

* The change was graded on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition.

The incidence of bronchiectasis, which was present in 3 patients, was not striking, and the lesions of this condition in our patients were in no way distinctive.

The incidence of emphysema in 3 patients and of bronchitis in 1 appeared to have been purely coincidental.

The occurrence of fat embolism in patients of this series was to be expected, for the literature contains a number of instances of death from this cause among rheumatoid patients.[7] A common accompaniment of rheumatoid arthritis is epiphysial osteoporosis, a condition which increases the likelihood of fat embolism, because fracture of the osteoporotic bone may release significant amounts of fat into the venous circulation. Such fractures may be incurred even during careful orthopedic or physical therapy manipulations. Such a train of circumstances probably took place in the 2 fatal instances in our series.

Hepatic Lesions.—The notable observations relating to the liver are outlined in table 3. A curious healing effect of hepatic injuries on rheumatoid arthritis

7. Rosenberg, E. F.; Baggenstoss, A. H., and Hench, P. S.: Unpublished data.

and fibrositis has been described by Hench.[8] We have not, however, found any hepatic lesions which could be considered specific for this disease.

Hypertrophy of the liver was moderately frequent, as indicated by the fact that the weight exceeded 1,800 Gm. in 8 adults. It was the result of chronic passive congestion in some and of fatty change in others. We did not encounter any evidence to suggest that the reticuloendothelial system was stimulated to proliferate in the liver as it is at times in the spleen and the lymph nodes of patients suffering from rheumatoid arthritis.

Ten livers weighed less than 1,600 Gm., indicating that atrophy of the liver was even more common than hypertrophy. It was associated with inanition and general visceral atrophy in 7 cases but was present without associated wasting of the body in 3 cases. In 6 of the 10 cases in which there was hepatic atrophy there was also chronic passive congestion of the liver, and we believe that the atrophy was caused by this long-standing chronic passive congestion.

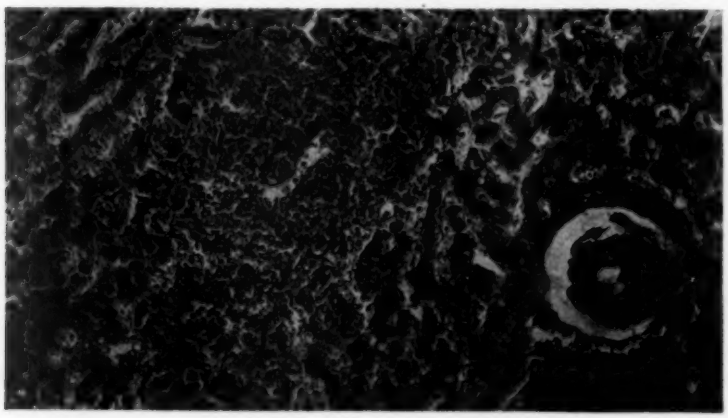

Fig. 1.—Liver. Mild chronic passive congestion with necrosis of cells about a central vein. So-called toxic central necrosis. Hematoxylin and eosin; × 120.

The incidence of chronic passive congestion of the liver was high, this condition being present in 18 cases. It reflected the high incidence of serious heart disease. The histologic preparations of the livers in these cases always disclosed atrophy of the parenchymal cells about the central veins. This atrophy had doubtlessly resulted from the passive congestion.

A significant degree of hepatic central necrosis (fig. 1) affecting parenchymal cells was observed in 4 instances. This central necrosis was always associated with rheumatic heart disease and with severe and extremely crippling rheumatoid arthritis. We have no definite information as to whether any of the 4 patients had taken drugs containing cinchophen. The deaths of 2 had been caused by rheumatic heart disease, the death of a third by bronchopneumonia and that of the fourth by bronchiectasis and pulmonary suppuration. None of these factors alone explains satisfactorily the presence of hepatic necrosis, but we must admit the possibility that damage to the liver might have been caused by these diseases or by some remedy which may have been taken for the rheumatism.

Some degree of hepatic fatty change was observed in 7 cases. As we reviewed our data in search of an explanation we found that this lesion was associated

8. Hench, P. S.: M. Clin. North America **24**:1209, 1940.

with an acute infection in 5 cases: bronchopneumonia in 2, pulmonary suppuration and bronchitis in 1, acute pyelonephritis in 1 and abscesses in the prostate in 1. In 3 further cases hepatic fatty change was associated wtih extremely severe clinical forms of rheumatoid arthritis as well as with rheumatic heart disease. In 2 cases, however, fatty change was associated with only moderate grades of rheumatoid arthritis and with no other serious visceral lesions. We therefore considered that fatty change might have reflected only the poor nutritional status of the patients during the days immediately preceding death, but it is possible that fatty change in the liver has a more direct significance in relation to rheumatoid arthritis.

Lesions which we identified as "serous hepatitis" [9] were observed in 9 cases. Usually we found this associated with some degree of passive congestion and atrophy of liver cells. Histologically, serous hepatitis is a separation of the reticulum fibers from the liver cells. Its significance is unknown. It may possibly result, as an artefact, from shrinkage of tissues during fixation and dehydration and thus may not have pathologic significance. We could not correlate this lesion with the severity or with the duration of the arthritis.

TABLE 4.—*Postmortem Observations on the Lymph Nodes in Seventeen Cases of Rheumatoid Arthritis*

	Cases
Proliferation of reticuloendothelial cells in sinuses	7
Proliferation of reticuloendothelial cells in follicles	1
Suppurative lymphadenitis (2 cases)	
Left inguinal nodes	1
Peripancreatic nodes	1
Degeneration of secondary centers of lymph follicles	2
Amyloid deposits	2

Lymph Nodes.—The lymph nodes, like other viscera, failed to reveal any lesion which could be considered pathognomonic of rheumatoid arthritis. Our findings as a result of a study of the lymph nodes in 17 of the cases are summarized in table 4.

Our series does not include any cases in which striking generalized enlargement of lymph nodes had been present during life. Moderate hypertrophy of lymph nodes such as we encountered has long been a recognized accompaniment of rheumatoid arthritis. Generally it is found in nodes which drain regions where there are affected joints, but occasionally all nodes are enlarged, and in some instances the spleen and the liver are also clinically enlarged. Notable descriptions of the association of enlargement of the spleen, the liver and lymph nodes with rheumatoid arthritis are those of Chauffard and Ramond,[10] Herringham,[11] Still,[12] Kauffman,[13] Collins,[14] Felty [15] and Hanrahan and Miller.[16]

9. Rössle and Eppinger, cited by Klemperer, P., and Keschner, H. W.: Am. J. Path. **12**:797, 1936.
10. Chauffard, A., and Ramond, F.: Rev. de méd., Paris **16**:345, 1896.
11. Herringham, W. P.: Clin. J. **34**:257, 1909.
12. Still, G. F.: Med.-Chir. Tr., London **80**:47, 1897.
13. Kauffman, D. E.: J. Missouri M. A. **34**:157, 1937.
14. Collins, D. H.: Rep. Chron. Rheumat. Dis. **3**:49, 1937.
15. Felty, A. R.: Bull. Johns Hopkins Hosp. **35**:16, 1924.
16. Hanrahan, E. M., Jr., and Miller, S. R.: J. A. M. A. **99**:1247, 1932.

The histologic observations in our own cases were in essential agreement with those noted in previous descriptions. The lesion which we noted most commonly and which has been reported repeatedly in the past was hyperplasia of the reticuloendothelial cells both within sinuses and within follicles.

Suppurative lymphadenitis of the inguinal nodes was noted in 1 case of cellulitis of the leg, and suppurative lymphadenitis of the peripancreatic nodes was found in another case in which we could not find any cause for this lesion.

Cellular degeneration of secondary centers of lymph follicles was noted in 2 cases. This condition is of uncertain cause. Amyloid deposits were present in 2 cases.

The Spleen.—Notable observations regarding the size of the spleen and the lesions present are assembled in table 5. Our studies of the spleens have failed to reveal any pathognomonic lesions characteristic of rheumatoid arthritis. We have noted that a significant enlargement of this organ was present in approximately 58 per cent of the patients (weight more than 200 Gm. in 14 of the 24 cases in which the weight of the spleen was known). This increased splenic weight was apparently caused by chronic passive congestion in 6 cases, and by

TABLE 5.—*Postmortem Observations on the Spleen in Thirty Cases of Rheumatoid Arthritis*

	Cases
Mean weight (24 cases) ..... 250 Gm.	
Lightest ..... 86 Gm.	
Heaviest ..... 573 Gm.	
Weighing 150-199 Gm.	6
Weighing 200-299 Gm.	5
Weighing 300 Gm. and more	9
Chronic passive congestion	8
Reticuloendothelial hyperplasia	5
With atrophy of malpighian corpuscles	2

reticuloendothelial hyperplasia in 5. We were interested to note, however, that histologic studies of 3 large spleens (323, 335 and 345 Gm.) did not show anything of note. The greatest weight, 573 Gm., was encountered in the spleen of a patient who had had severely deforming rheumatoid arthritis and whose death had resulted from pulmonary fat embolism. The outstanding histologic abnormality of this spleen was proliferation of the reticuloendothelial cells.

The incidence of chronic passive congestion of the spleen was high (present in 8 cases, or 27 per cent), but one might compare this incidence to that in the liver, for in both a high incidence of chronic passive congestion could be directly related to severe heart disease and congestive failure.

Degenerative changes within the bodies of the malpighian corpuscles were noted in 5 cases and similar degenerative changes in secondary centers of the lymph nodes were noted in 2 instances. These changes have a nonspecific character which pathologists encounter in a great variety of circumstances and which we believe cannot, with present knowledge, be related specifically to rheumatoid arthritis.

In 2 cases of this series amyloid degeneration of the spleen and other organs was found to be associated with the rheumatoid arthritis. One of the patients, a man of 48 years, who had had rheumatoid arthritis of many joints for six years, also had amyloid disease involving the spleen, liver, kidneys, adrenal glands, esophagus, small intestine, bladder, lymph nodes and thymus. Associated lesions

were chronic rheumatic mitral endocarditis, chronic rheumatic aortitis and focal myocarditis, ascites (300 cc.) and bilateral hydrothorax (500 cc.). The other patient, a boy of 17 years, who had had rheumatoid arthritis for seven years, had amyloidosis of the spleen, kidneys and lymph nodes. Associated lesions were subacute rheumatic pericarditis and focal myocarditis, cardiac hypertrophy (425 Gm.—normal 225 Gm.) with dilatation of the left ventricle and fatty change of the myocardium, subacute duodenal ulcer, bilateral hydrothorax, emaciation of grade 3 and chronic suppurative prostatitis.

Kidneys.—Notable observations regarding the kidneys of the patients included in this series are assembled in table 6. In the kidneys, as in most of the other organs which we examined, we failed to find any specific lesion which could be designated as characteristic of rheumatoid arthritis. However, we were impressed by a high incidence (19 cases) of glomerular endothelial proliferation (fig. 2 *A* and *B*), a lesion which Bell [17] designated a form of glomerulitis. The clinical studies in these cases revealed that frequently the patients excreted urine containing light or, rarely, heavy traces of albumin. However, severe renal insufficiency did

TABLE 6.—*Postmortem Observations on the Kidneys in Thirty Cases of Rheumatoid Arthritis*

	Cases
Glomerulitis (19 cases)	
Grade 1	13
Grade 2	6
Chronic or subacute interstitial nephritis (pyelonephritis) (4 cases)	
Subacute suppurative pyelonephritis	3
Chronic nonsuppurative pyelonephritis	1
Amyloid degeneration	2
Nephrolithiasis with acute pyelitis	1
Dissecting aneurysm, right renal artery	1

not result in any of these instances. We suspect, therefore, that the glomerulitis was responsible for the traces of albumin in the urine.

Bell, whose studies of this glomerular lesion have been exhaustive, expressed the belief that it may result from irritation of glomerular capillaries by a variety of toxic substances, especially those derived from streptococci. With this opinion in mind it is of interest to note that among our 19 cases showing this lesion the infectious processes present were as follows: terminal bronchopneumonia in 6, chronic pulmonary suppuration in 3 and active or healed rheumatic endocarditis in 9. Since Bell found that only 18.8 per cent of patients dying of pneumonia had glomerulitis, one would not expect that the terminal bronchopneumonia present in our patients would result in a high incidence of glomerulitis. Moreover, 3 patients in whom we found this form of glomerular inflammation had neither suppurative foci nor any evidence of rheumatic heart disease. These considerations led us to suspect that the agent responsible for rheumatoid arthritis may also be responsible for low grade, essentially subclinical glomerulitis.

A notable association between typhoid vaccine shock therapy and fatal diffuse severe pyelonephritis associated with anuria was seen in 2 instances (fig. 2 *C*). Neither of the 2 patients had shown any evidence of pyelonephritis before the typhoid vaccine was administered, and we have no satisfactory explanation for this

17. Bell, E. T.: Am. J. Path. **12**:801, 1936.

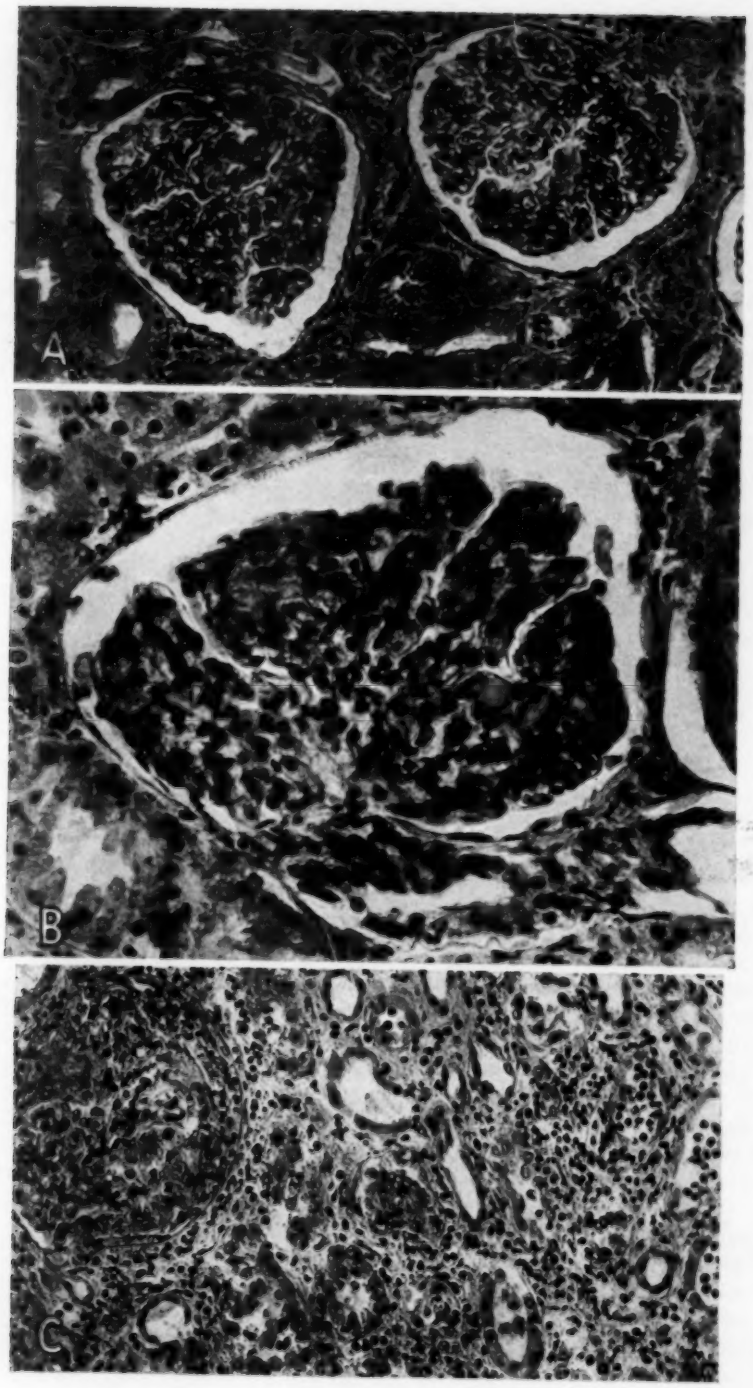

Figure 2

(See legend on opposite page)

curious untoward reaction to shock therapy. We consider this lesion to be a serious but fortunately very rare complication of treatment with typhoid vaccine.

There were 2 cases in which the glomeruli of the kidneys were the seat of amyloid deposits.

Other renal lesions are of only passing interest and represented probably only accidental associations with the rheumatoid arthritis. These included the following: dissecting aneurysm of the right renal artery which led to thrombosis of the artery and infarction of the kidney (1 case) and nephrolithiasis, associated with acute pyelitis (1 case).

Gallbladder.—Lesions found in the gallbladder included chronic cholecystitis in 2 cases (associated with stones in 1 case), uncomplicated cholelithiasis and acute purulent cholecystitis, each in 1 case. No relation of these lesions to rheumatoid arthritis was demonstrated.

Gastrointestinal Tract.—Various lesions were observed in the gastrointestinal tract, but for the most part these did not have any bearing on the arthritis. One patient who had generalized amyloidosis was found to have some amyloid deposited in the gastrointestinal tract. Other notable gastrointestinal lesions included ulcerative esophagitis (3 instances) and chronic ulcer, acute erosion and polypoid carcinoma of the stomach (1 instance each). Scars of healed duodenal ulcers were detected in 2 cases. A localized region of chronic inflammation in the small intestine was present in 1 instance. A few acute ulcers were observed in the colon of 1 patient and mild colitis without ulceration was seen in another.

Pancreas.—No pancreatic lesions were encountered which could be related in any significant way to rheumatoid arthritis. In 3 instances we found moderate degrees of chronic interstitial pancreatitis. In 1 of these 3 cases we encountered fat necrosis. The origin of these lesions is obscure; they are found in association with many other conditions. A moderate amount of fatty replacement was found in 3 additional cases.

Adrenal Glands.—The adrenal glands also failed to show any lesions which we could designate as a specific result of the rheumatoid arthritis. In 3 cases we found chronic passive congestion and considered this to be an accompaniment of severe heart disease. Focal collections of lymphocytes were encountered in the cortex in 1 case (a lesion fairly commonly present in occasional necropsies on persons who have died of varying causes). Amyloid deposits, atrophy, hemorrhage and periadrenal arteritis were observed each in 1 instance. We considered these lesions to be coincidental.

Thyroid Gland.—As one might expect, we encountered adenoma of the thyroid gland in a few (4) of the patients. Colloid goiter was noted in 4, and mild parenchymal hyperplasia was observed in 2. These lesions too were doubtlessly coincidental.

EXPLANATION OF FIGURE 2

A, kidney. Endothelial proliferation (glomerulitis) grade 1 and hyaline granular degeneration of convoluted tubules. Hematoxylin and eosin; × 205.

B, kidney. Glomerulitis grade 2. The capillaries are filled by a pronounced proliferation of endothelial cells. Hematoxylin and eosin; × 350.

C, kidney. Suppurative interstitial nephritis (pyelonephritis) with involvement of a glomerulus. Hematoxylin and eosin; × 190.

Prostate.—Lesions encountered in the prostate glands of the male patients in this series were considered by us to be coincidental and not directly related to the rheumatoid arthritis. Chronic suppurative prostatitis was found in 2 cases, and in 1 we encountered carcinoma.

Blood Vessels.—We examined the visceral blood vessels of these subjects with particular care because many of the clinical phenomena of rheumatoid arthritis indicate abnormal functioning of the vascular system. Thus, many of the patients suffer with tachycardia, cyanosis, abnormal sweating and discolorations of the extremities like those seen in Raynaud's disease. Despite these symptoms and despite the fact that we paid particular attention to the question of lesions in blood vessels, we have little to report in the way of significant findings in that system. As one might expect, in this group of relatively young persons we found arteriosclerosis to be of only moderate degree in general. In 20 of the patients the arteriosclerosis of the aorta was graded 1 (on the basis of 1 to 4); in 9 it was graded 2, and in only 1 case was it graded 4.

There was no widespread characteristic change among the smaller arteries or arterioles, and we did not find any significant lesions in the venous system which might be designated as a phenomenon of the rheumatoid arthritis.

COMMENT

The outstanding feature of the postmortem examinations of these patients was the finding of a high incidence of rheumatic heart disease. We have commented extensively on the finding in previous papers, and we believe it significant that among 5 patients who have been added to this series since the foregoing report was published we found certain rheumatic heart disease in 2 and a cardiac lesion which was possibly rheumatic in origin in 1. We have been interested to note that the publication of our paper was followed quickly by confirmatory reports of other postmortem studies in which a high incidence of rheumatic heart disease was found in patients suffering from rheumatoid arthritis.[18] This accumulating evidence of the high coincidence of the two conditions is becoming more and more impressive and suggests ever more strongly that rheumatoid arthritis and rheumatic fever are in some manner closely related conditions. The results of our study again focus attention on the researches of Klinge,[19] who concluded that rheumatoid arthritis and rheumatic fever are different manifestations of the same disease.

Second only in importance to the observations which we have reported concerning the hearts is the finding among the kidneys of these patients of a strikingly uniform and frequently present glomerulitis. This lesion was not extensive but it occurred with such frequency that we have had to conclude it is in some manner a sequel of, or accompaniment of, the disease of the joints. We considered the possibility that

18. Andrus, F. C.: Minnesota Med. **24**:1071, 1941. Fingerman, in discussion on Andrus, F. C.: ibid. **24**:1072, 1941. Dawson, H., and Bennett, G. A.: Unpublished data.

19. Klinge, F.: Jahresk. f. ärztl. Fortbild. **24**:1, 1933.

the glomerulitis might have resulted from the effects of other toxic or infectious states, and we feel certain that in some of the cases chronic pulmonary suppuration, and in others rheumatic infections, were responsible. We found the glomerulitis in some cases, however, without other discernible toxic or infectious process than rheumatoid arthritis.

Ever since the latter years of the nineteenth century, when Still [12] and Chauffard and Ramond [10] described the association of splenic and lymph node enlargements in cases of rheumatoid arthritis, pathologists and clinicians have been keenly interested in the changes which appear in these organs among arthritic patients. The consensus has been that no pathognomonic lesions appear in these organs, and our material also failed to disclose any characteristic lesions in the lymphatic system. Although some enlargement of the spleen was encountered commonly, we were forced to attribute this enlargement in most instances either to chronic passive congestion or to nonspecific proliferation of the reticuloendothelial tissues.

With few exceptions, the anatomic changes which we encountered in the liver did not appear of sufficient gravity to have affected the known or clinically measurable functions of the liver. Chronic passive congestion and fatty change were the lesions most commonly encountered.

The results of our anatomic investigations have not led us to any final conclusions regarding the causation of rheumatoid arthritis. In general, the frequent evidence of inflammatory processes, such as we found in the hearts and the kidneys, together with the hyperplasia of the spleen and lymph nodes, favors the hypothesis that rheumatoid arthritis must be caused by some low grade infective agent. The presence of amyloidosis in 2 cases and the occasional presence of inflammatory lesions in the intestinal tract, the pancreas, the adrenal bodies and the prostate and even in the lungs might also be considered to favor that view.

Our data support the conception of rheumatoid arthritis as a generalized disease affecting not only the joints but also many viscera. However, we have been disappointed in general to find it necessary to arrive at the conclusion that our study has not cleared in any discernible manner the mystery surrounding the cause of the disease.

SUMMARY

Clinical records and necropsy data on 30 patients suffering from rheumatoid arthritis have been reviewed with a view to determining the nature of the visceral lesions in patients suffering with this disease.

Observations on the heart indicated that rheumatic cardiac disease was present in 16 patients (53 per cent) and cardiac lesions other than rheumatic in 8 (27 per cent).

The pulmonary diseases present among these patients included, notably, bronchopneumonia, fibrous pleuritis, bronchiectasis, pulmonary embolism and fat embolism. The interrelation of these pulmonary diseases with the rheumatoid arthritis has been reviewed.

Study of the liver failed to reveal any characteristic lesion which we could ascribe to rheumatoid arthritis. A number of abnormalities noted included hypertrophy, atrophy, chronic passive congestion, fatty change, central necrosis, amyloid deposits, subacute yellow atrophy, healed miliary tuberculosis and the serous hepatitis of Rössle and Eppinger.[9]

The lymph nodes and the spleen, though occasionally enlarged during life, were found to show only various nonspecific inflammatory and degenerative effects. These included proliferation of reticuloendothelial tissues, degeneration of lymph follicles, amyloid deposits, suppurative lymphadenitis, hypertrophy (of the spleen) and chronic passive congestion.

A striking result of this study was the finding of low grade nonspecific glomerulonephritis in 19 of our cases. The implications of this lesion have been considered. Other renal lesions present among these patients included chronic or subacute interstitial nephritis, nonsuppurative pyelonephritis, amyloid degeneration, nephrolithiasis with acute pyelitis and dissecting aneurysm of the right renal artery.

Various lesions, mainly of minor importance, were encountered in the other organs. These have been reviewed and catalogued.

THE SHWARTZMAN PHENOMENON IN THE GENESIS OF PULMONARY ABSCESS

EXPERIMENTAL PRODUCTION OF ABSCESSES IN THE LUNGS OF RABBITS BY MEANS OF A STRAIN OF GRAM-NEGATIVE ANAEROBIC BACILLI, RESEMBLING BACILLUS NECROPHORUS, EMPLOYED AS A LUNG-PREPARATORY FACTOR, WITH NOTES ON SOME FACTORS CONCERNED IN PATHOGENICITY

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In 1932 one of us (John Cohen †) published studies of putrid abscess of the lung, attempting to define the bacterial factors in its genesis.[1] In 16 cases of putrid pulmonary abscess he found a mixture of anaerobes of various types, among which were the following; a nonhemolytic "micro-aerophilic" streptococcus (Streptococcus γ) and a pleomorphic anaerobic diphtheroid, which were cultured from the pus in all 16 cases; Bacterium melaninogenicum, found in 13 cases; B. ramosus, in 8; fusiform bacilli, in 6; Bacillus fragilis, in 4; Bacillus thetoides, in 2; Bacillus furcosus, in 2; Leptothrix, in 3; Vibrio, in 1; Clostridium cochlearium, in 1. Aerobes were infrequently grown: Streptococcus viridans in 2 cases; Friedländer's bacillus in 1. He mentioned the etiologic importance of bacterial synergism in pulmonary abscess. This possibility had, in fact, been under discussion since the publication of the early researches of Guillemot, Hallé and Rist, in 1904.[2] He also pointed out the favoring effect on the in vitro growth of B. melaninogenicum of symbiotic cultivation with Str. γ.

Cohen's subsequent studies led to his interest in the Shwartzman phenomenon as the underlying mechanism in the production of pulmonary abscess by these micro-organisms. The Shwartzman phenomenon[3a]

† Dr. Cohen died on Jan. 24, 1936.

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1. Cohen, J.: Arch. Surg. **24**:171, 1932.

2. Guillemot, L.; Hallé, J., and Rist, E.: Arch. de méd. expér. et d'anat. path. **16**:571, 1904.

3. Shwartzman, G.: Phenomenon of Local Tissue Reactivity, and Its Immunological, Pathological and Clinical Significance, New York, Paul B. Hoeber, Inc., 1937, (*a*) chap. 1, p. 1; (*b*) chap. 7, p. 186; (*c*) chap. 8, p. 222.

consists in severe hemorrhagic necrosis rapidly evoked in a tissue at the site of a previous parenteral introduction of one or another of certain bacterial filtrates (preparatory factor) following an intravenous injection, made eighteen to twenty-four hours afterward, of a toxin (provided it is potent) consisting of a filtrate of a culture of the same or of another bacterium (provocative factor). The conventional tissue for its elicitation is the rabbit's skin. It may be produced in the kidneys, the gastric mucosa, the appendix, the synovia of joints, certain tumors (without previous preparation), the adrenal gland, the pancreas, lymph nodes and the other tissues except the brain and the meninges.[3b, c] It was produced in the lung in 1929 by Shwartzman employing Bacillus typhosus filtrate intratracheally as the preparatory factor.[3b]

Cohen [4] attempted to produce a potent toxin by the use of filtrates from cultures of anaerobes isolated from putrid pulmonary abscesses. He described experiments in which each of these filtrates was inoculated intradermally as the skin-preparatory factor and subsequently intravenously as the provocative factor. Negative results were obtained with filtrates of pure cultures of these anaerobes. When a potent heterologous toxin (e. g., B. typhosus or meningococcus toxin) was substituted as the skin-preparatory factor, the anaerobic toxin elicited a high incidence (80 per cent) of positive cutaneous reactions when given intravenously, indicating its potency at least as a provocative factor. On the other hand, strong skin-preparatory potency was found in filtrates of cultures of B. melaninogenicum and Streptococcus γ grown in symbiosis (9 positive results in 22 instances).

Some indication of the nature of the elements concerned in bacterial pathogenicity is possibly suggested by these differences in skin-preparatory potency of bacterial filtrates. As stated by Cohen,[4] "Further work on the pathogenicity of the various organisms, to be reported, points to the interesting fact that only those organisms which give the positive Shwartzman phenomenon when they are grown in suitable culture mediums are also able to produce severe necrotizing lesions in the lungs of rabbits."

In subsequent studies (unpublished) Cohen studied the toxin production of several other anaerobic micro-organisms from the pus of human pulmonary abscess. In the case of one of these (referred to in his notes as no. 7) he demonstrated the truth of his assumption, i. e., that its capacity in pure culture to produce a potent skin-preparatory toxin can be correlated with its ability to produce severe necrotizing lesions in the lungs of rabbits. The present report deals with an application of the Shwartzman phenomenon in the study of the pathogenicity of this anaerobe in the production of pulmonary abscesses in rabbits.

4. Cohen, J.: J. Infect. Dis. **52**:185, 1935.

DESCRIPTION OF THE MICRO-ORGANISM

The anaerobic bacillus employed was isolated by Cohen from a human case of putrid abscess of the lung. For the details of its isolation and cultivation, the reader is referred to previous papers.[5]

Cultural Characteristics.—The micro-organism was one of a group of non-chromogenic, gram-negative, strictly anaerobic bacilli producing a foul odor in cultures. It varied in size in different mediums, appearing as coccoid or as slender straight or slightly curved bacillary forms 1 to 6 microns in length, with pronounced polar metachromatism. The body of the micro-organism stained faintly and seemed to have a slightly beaded appearance. Occasionally long curved threadlike forms were seen. It possessed no capsule or flagellum, was nonmotile and did not form spores. It grew best in freshly boiled, rapidly cooled mediums containing sterile rabbit blood. The colonies on anaerobic blood agar plates were mucoid, grayish and opalescent, and produced hemolysis. Moreover, when the micro-organism had been planted on blood agar plates and incubated aerobically, hemolysis could be detected even in the absence of visible growth. Cultures in fluid and semisolid mediums with and without blood gave off a putrid odor. Growth occurred in gelatin with a flocculent sediment, but the gelatin was not liquefied. Indol was produced in the usual test mediums. Hydrogen sulfide was not formed. Milk was peptonized but not coagulated. Litmus milk was partly decolorized. Gas and acid were produced by this micro-organism in a semisolid medium containing dextrose and maltose. Lactose, sucrose and mannite were apparently unaffected.

The micro-organism grew best at 37 C. but grew also at room temperatures. Its viability was maintained in the presence of bile, but its virulence for rabbits was reduced greatly (see subsequent section). Its virulence was also reduced by exposures to air for relatively short periods (see subsequent section).

Pathogenicity.—A subcutaneous injection of a virulent culture into the groin of a rabbit was followed in two days by a localized firm swelling which contained a large, sharply circumscribed area of soft white cheesy necrosis. Histologically, the area of necrosis had a granular amorphous appearance with much basophilic nuclear debris. It was sharply demarcated by an outer zone of acidophilic necrosis. The surrounding connective tissue and muscle were edematous and infiltrated with moderate numbers of polymorphonuclear and mononuclear leukocytes. Small areas of necrosis were occasionally found in the liver after subcutaneous inoculation of a virulent culture. Injections into mice were followed by similar sharply circumscribed necrotic lesions. Intratracheal injections into the lungs of rabbits were almost uniformly followed by necrotic lesions of a specific type. These are described in detail in a subsequent section.

Classification of the Micro-Organism.—From the foregoing description it is difficult to establish the exact taxonomic relationships of the bacillus. In many respects it resembles closely B. necrophorus (Schmorl), according to descriptions of the latter as collated from many sources by Weinberg.[6] The essential features of B. necrophorus are its polymorphism and metachromatic staining, its vitality under unfavorable conditions of cultivation in artificial mediums, its

5. Cohen (footnotes 1 and 4).

6. Weinberg, M.; Nativelle, R., and Prévot, A. R.: Les microbes anaérobies, Paris, Masson & Cie, 1937.

decolorization of litmus milk with slow curdling, its failure to attack gelatin, its production of indol and failure to produce hydrogen sulfide, and its fermentation of sugars. The pathogenicity of B. necrophorus for rabbits and mice is marked, according to Weinberg, the characteristic process being putrefactive necrosis at the site of local infection, followed by necrotic lesions of the viscera, especially the liver and the lungs, the bacillus being transported via the blood stream. As stated by him, the "abscesses" are rarely simply suppurative but are usually gangrenous in type, giving rise to the typical classic appearance of "necrobacillosis of the liver or lung." Other animals are less susceptible. It has been isolated from various gangrenous lesions in man,[7] one of the first recorded cases of its isolation being that from necrotic pharyngitis and pneumonia in an infant (Ellerman[8]). It has been found in gangrenous stomatitis, subcutaneous phlegmonous inflammation, puerperal infection, ulcerative colitis and erosive balanitis.[6] Shaw[9] found it in the pus of a pulmonary abscess.

Beveridge[10] studied twelve strains of B. necrophorus and found two serologic groups. Minor variations among the strains were found in the fermentation of sugars, the coagulation of milk or serum and the viability on exposure to air. As also noted by others, the histologic features of the lesions were characteristic for the species. Although the organism was highly pathogenic for rabbits, its pathogenicity for other animals was variable, and it often figured merely as a saprophyte. Its pathogenicity in guinea pigs and human beings was greatly enhanced when it occurred in association with other micro-organisms, such as cocci (Schmorl[11]). According to Beveridge, its ability to produce lesions appeared to be largely due to the necrosing properties of its endotoxin.

EXPERIMENTAL METHODS

Method of Intratracheal Inoculation.—The rabbits employed were of healthy stock, weighing 1.5 to 2.5 Kg. The ventral region of the neck was shaved, and a depilatory was applied to remove the last vestige of hair. The animal was tied to a board with its ventral surface up and its head held back to expose the shaved surface. No anesthetic was employed. Iodine was used for disinfection of the skin, and sterile technic was observed throughout. A linear incision was made over the trachea. The needle of a syringe containing the inoculum was gently insinuated between two rings and the desired amount of the inoculum was forced into the trachea; the needle was then quickly withdrawn, a metal clip or a single silk suture applied to the edges of the skin for approximate closure and the rabbit quickly lifted by the ears to prevent passage of the fluid into the pharynx and nose. The animal was then gently swung from side to side, and its thorax was patted with the hand, to insure a flow of the injected liquid into the lower areas of the lung.

Methods of Examination of Postmortem Material.—At suitable intervals after inoculation, the rabbits were killed by injection of 20 cc. of air into the marginal vein of the ear, and the thorax was opened under aseptic conditions.

7. Cunningham, J. S.: Arch. Path. **9**:843, 1930. Shaw, F. W.: Zentralbl. f. Bakt. (Abt. 1) **129**:132, 1933.

8. Ellerman, V.: Zentralbl. f. Bakt. (Abt. 1) **38**:383, 1905.

9. Shaw, F. W., and Bigger, I. A.: J. A. M. A. **102**:688, 1934.

10. Beveridge, W. I. B.: J. Path. & Bact. **38**:467, 1934.

11. Schmorl, cited by Beveridge.[10]

The lungs and the mediastinal structures, including the heart, were removed in one piece and kept in a sterile Petri dish until aerobic and anaerobic cultures had been made. Following this the organs were dissected and the gross findings noted, and material was taken for histologic study, a 4 per cent solution of formaldehyde being used as fixative.

Preparation of an Inoculum of Fixed Virulence.—Rabbits were inoculated subcutaneously in the groin with 1 to 2 cc. of a viable culture. The production of a large swelling signaled the formation of an abscess containing large numbers of the bacteria of enhanced virulence. Aspirated material was inoculated into Smith-Noguchi medium containing 1 cc. of sterile defibrinated rabbit blood. The former was prepared by adding to ascitic fluid 1 per cent dextrose and 1 per cent broth; 10 cc. of the mixture was poured into a long narrow test tube, 20 by 1.5 cm., and a piece of fresh sterile rabbit kidney was added. The tube was incubated overnight to make certain of its sterility. After inoculation of the medium with the anaerobe, sterile petrolatum was added and the tube incubated for forty-eight hours. At the same time blood agar plates of p_H 7.4 were also inoculated with a drop of the same culture and incubated aerobically and anaerobically for the same period of forty-eight hours, to rule out contamination by other micro-organisms.

CONTROL STUDIES EMPLOYING FULLY VIRULENT CULTURES: THE PATHOGENIC MECHANISM

In the original experiments, lesions were produced in 23 of the 27 rabbits given intratracheal injections of 2 cc. of the forty-eight hour culture just described. In later experiments a similarly high incidence of lesions was obtained with the same strain of anaerobes after it had been carried in subculture for nearly eight years. Morphologically, the lesions in the lungs caused by the original culture and those caused by the subculture were identical.

Specimens were obtained at varying intervals after intratracheal inoculation. The lesion caused by this anaerobe had a characteristic appearance, which made its recognition easy at a glance as early as twenty-four hours after inoculation. Its evolution was fairly consistent, and an approximation of its age was often possible on the basis of the morphologic features alone. For purposes of description the five day stage is selected as embodying the salient features in their most typical form.

In the unopened lung the specific lesion was detected as a sharply circumscribed, raised consolidation, lobular or sublobar in extent, bulging at one or more points on the pleural surface (fig. 1). In most instances it was solitary; in the remaining ones it appeared in closely grouped or confluent areas of consolidation involving one or more lobes, homolaterally or bilaterally. The pleural surface was covered with grayish fibrin and presented beneath this a dirty, grayish white discoloration where the underlying lesion had extended to the surface. Congestion and hemorrhage were seen within these areas and peripherally, setting off the lesion from the surrounding uninvolved regions.

On cut section (fig. 2*A*) the sharp demarcation of the lesion was clearly disclosed. The lesion appeared in various sizes and shapes, often with a serpiginous outline but with a general tendency to assume a pyramidal shape with the base at the pleura. Separate areas appeared to be all of the same age. Two zones could be distinguished in the lesion, an outer compact zone, more nearly solid and of a pearly white color, and an enclosed softer area of darker

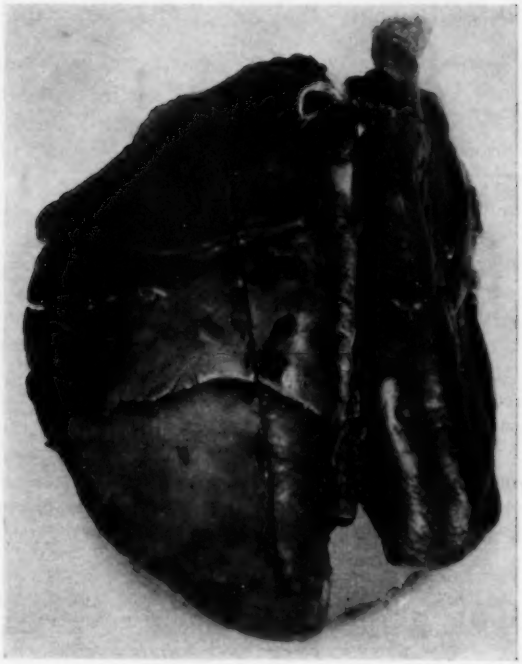

Fig. 1.—Rabbit lung exhibiting a typical lesion. This was seen five days after intratracheal injection of a virulent culture. Note the uniform consolidation extending to the pleura.

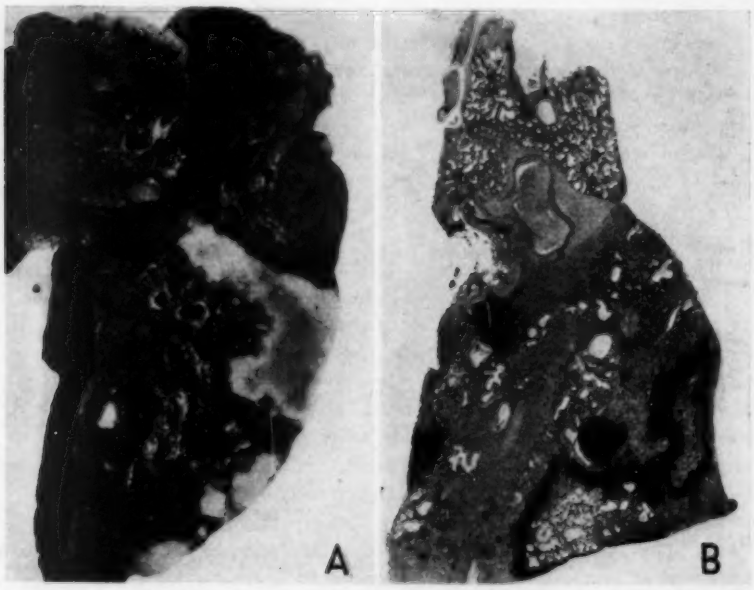

Fig. 2.—*A*, rabbit's lung opened to show the sharp demarcation of the specific lesion. Note the zonulation (marginal dense white zone with inner area of softening); *B*, low power photomicrograph of the specific lesion (hematoxylin-eosin stain).

color. The surrounding parenchyma presented a zone of congestion, edema and slight consolidation, fading gradually into normal tissue.

The histologic features corresponded well with the macroscopic observations. In each rabbit the lesion was of uniform development in all parts, apparent not only in separate areas of involvement but also in the various components of the individual lesion. In the parenchyma intervening between separate lesions or between separate portions of a large single lesion there were no evidences of continuing extension of the process. Nor were metatases found. It was clear that the final extent of the lesion had been determined in its early stages, probably as a result of rapid demarcation.

In addition to the sharp demarcation of the lesion, its other principal histologic features were its dense outer margin of leukocytic exudation and its uniform necrosis.

The marginal zone of leukocytic exudation produced the most marked tinctorial change in the sections. This zone was about 0.5 to 0.7 mm. in width in typical areas and was deep purple with the hematoxylin-eosin stain because of the compact infiltration of polymorphonuclear leukocytes. The polymorphous character of the lesion was therefore best appreciated from this zone, which outlined the lesion much as colored boundaries outline geographic areas on a map (fig. 2 *B*). Under higher magnification (fig. 3 *A*) the exudate within this zone appeared as dense plugs of necrobiotic and necrotic leukocytes filling the lumens of collapsed necrotic alveoli. Fibrin and hemorrhage were scanty or lacking.

A narrow line of acidophilic necrosis formed the outermost zone of the lesion. It measured 0.3 mm. or less in width and in places was barely recognizable.

Coarser structures, e. g., bronchi, larger blood vessels and fibrous septums, which passed across the separate zones of the lesion underwent changes corresponding to each zone successively traversed (fig. 3 *B*).

The large island of inflamed parenchyma enclosed by these zones exhibited simple ischemic necrosis, in which the alveolar framework was well preserved and the capillaries and the larger blood vessels were patent. The bronchioles were patent, but the alveoli were moderately atelectatic. These structures except for a basophilic nuclear debris were faintly eosinophilic. Erythrocytes were laked. Scattered necrotic leukocytes were seen, but there was no marked exudation of leukocytes such as that seen in the marginal zones of the lesion.

None of these features was found in the remaining lung tissue. The latter appeared essentially normal except for a few areas of mild atelectasis. The parenchyma immediately adjacent to the lesion presented changes of minimal degree, consisting of mild atelectasis with proliferation and vacuolation of alveolar epithelium, slight edema and few leukocytes.

Evolution of the Specific Lesion.—As early as five and one-half hours after intratracheal inoculation, patchy red consolidation in the lung was detected. Histologically, there was dense leukocytic exudation within numerous areas of atelectasis. The alveolar septums showed beginning acidophilic necrosis, and necrobiotic changes were seen in some of the leukocytes and proliferated alveolar phagocytes. The most intense exudation was associated with the most extensive atelectasis. The cause of the latter was not evident inasmuch as the bronchi and larger bronchioles were widely patent and almost entirely free of exudate or other material. There were no recognizable traces of the fluid inoculum intro-

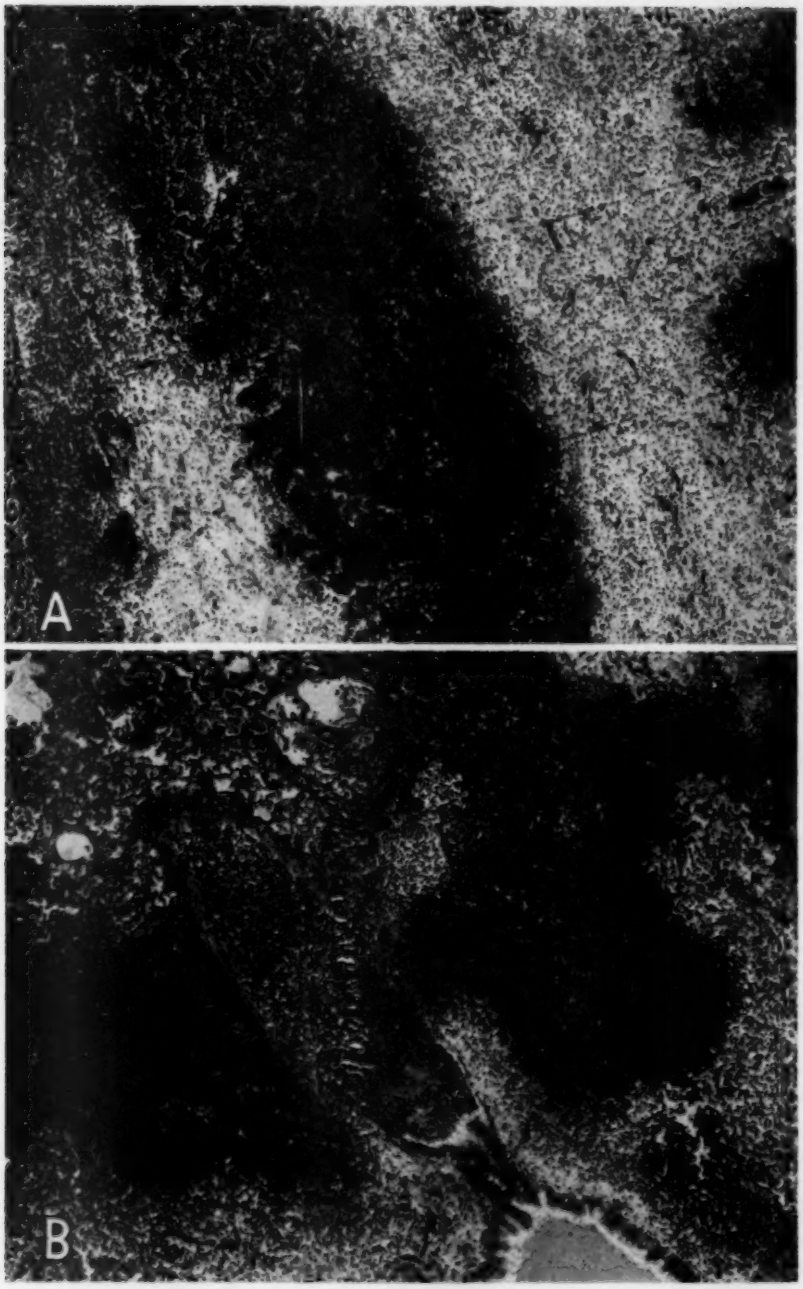

Fig. 3.—*A*, photomicrograph showing the dense leukocytic infiltration of the marginal zone of the lesion and ischemic necrosis of the enclosed parenchyma; *B*, photomicrograph showing involvement of a small bronchus at its point of emergence through the marginal zone.

duced intratracheally, and it was impossible to detect the particulate elements (bacteria) of the inoculum in the areas of consolidation.

Twenty-four hours after inoculation the lungs had well marked areas of consolidation bulging on their pleural surfaces at one or more points. In shape, distribution and size, these conformed to the description of the typical lesion given previously. The color was dusky purplish red, with relatively little of the grayish tinge seen in later lesions. They were less firm in texture than the latter and were less elevated above the pleural surface or the cut surface. The pleura was mottled red and lusterless.

Histologically, the lesion, whether solitary or multiple, presented the typical sharp demarcation. Three principal elements could be defined at this stage: (*a*) atelectasis, (*b*) leukocytic exudation and (*c*) necrosis.

Atelectasis, both patchy and confluent, appeared to be a constant feature. Leukocytic exudation or necrosis was mild or absent where atelectasis was slight and correspondingly marked where atelectasis was conspicuous. The necrosis was of less uniform extent than the exudation of leukocytes, and both processes ended abruptly in a sharp outer line of demarcation. The type of necrosis in the enclosed areas differed from that in the marginal zone, appearing to be the direct result of the ischemia caused by the choking of the alveolar capillaries and other nutrient blood vessels within the zone of marginal necrosis.

In the three day old lesion all the elements of the specific lesion were clearly defined. These comprised the marginal leukocytic zone, the central enclosed area of ischemic necrosis and the acidophilic necrosis involving the marginal zone, as well as the narrow line of demarcation beyond.

In older lesions, nuclear chromatolysis of leukocytes was further advanced, and slight organization appeared in the surrounding parenchyma. In some animals a considerable pleural empyema was found on the seventh day.

In 2 animals that lived about four weeks, the entire lesion underwent liquefaction and took the form of an encapsulated abscess from which the bacillus was recovered in pure culture.

Analysis of the Pathogenic Mechanism.—(*a*) Role of Atelectasis: The high incidence of positive results following single intratracheal inoculations of cultures of this strict anaerobe bears witness to the microorganism's ability to create for itself an anaerobic environment within the lung. It is of interest, therefore, that the initial phases of the lesion were characterized by atelectasis, which determined its ultimate size and shape and which formed the matrix for the leukocytic exudation and the necrosis. As a rule the bronchi and larger bronchioles were found widely patent. From the standpoint of morphology alone it was not possible to draw any conclusions regarding the mechanism of the atelectasis, i. e. whether the collapse was caused by simple mechanical blockage or by reflex bronchiolar spasm in response to some irritant. The occurrence of atelectasis within the first few hours after intratracheal injection of the inoculum and the equally early occurrence of leukocytic exudation and beginning necrosis indicate that the anaerobe was endowed with pathogenic properties at the moment of transfer from the culture

tube to the lung tissue, even before its viability within the lung was demonstrable. It was deduced that its survival and activity in producing a specific pulmonary lesion were probably bound up with its ability to bring about immediate atelectasis. To test this hypothesis further, the following experiments were carried out (1941):

1. Forced inhalation of carbon dioxide. Each of 4 rabbits was given a large dose (4 cc.) of the inoculum intratracheally. At thirty minute intervals the animals were made to inhale a fairly high concentration of carbon dioxide mixed with air for about ten minutes. In each case respiration appeared quicker or deeper or both. The procedure was repeated ten or twelve times. The animals were killed and the lungs examined in the usual manner. In 3 animals no important differences were found in the type or the extent of the lesions except that grossly the lungs appeared slightly fluffy and the lesions appeared small and frequently confined to the hilus and deeper portions of the lungs. In the fourth rabbit small scattered areas of consolidation were found which on histologic study were found to be areas of dense atelectasis with only trifling leukocytic exudation or necrosis.

2. Forced inhalation of oxygen (95 per cent) and carbon dioxide (5 per cent). Four more rabbits were subjected to the same procedure except that a mixture of 95 per cent oxygen and 5 per cent carbon dioxide was substituted for the mixture of carbon dioxide and air. In 1 rabbit the lungs appeared normal at autopsy. In the others the lungs were uniformly well inflated and of normal color except for a few small scattered areas of dark red consolidation. The latter when examined histologically varied considerably. In 1 rabbit a few of these areas presented the typical necrotic lesion, while others were composed of densely atelectatic alveoli in which the lining epithelium had begun to swell and desquamate. In another rabbit a single small necrotic lesion and several areas of consolidation of atelectatic type were seen. In the fourth rabbit the areas of consolidation were all of the atelectatic type except for a few minute foci of leukocytic exudation and beginning necrosis.

In a subsequent experiment 6 rabbits were inoculated in this manner and supplied with the same mixture of oxygen and carbon dioxide, but these animals rebreathed the mixed gases from an improvised rubber mask (a thin rubber glove was employed) under mildly positive pressure. Treatments were begun thirty to sixty minutes after inoculation and were maintained for ten minutes and repeated one to three times afterward at varying intervals. The positive autopsy findings in these rabbits were even less marked than those in the preceding series. In 3 rabbits minute patches of dark red atelectatic consolidation were the only finding; in 2 others microscopic foci of necrosis were present in addition. The sixth rabbit was found dead, and the lungs showed merely hypostatic congestion and edema. In none of these animals was the specific lesion recognizable grossly.

(*b*) Role of Bacterial Toxic Factors: As mentioned, Cohen [4] studied this and other anaerobes isolated from putrid abscesses of lungs for toxins capable of eliciting the Shwartzman phenomenon in the rabbit's skin. He further established a correlation between the capacity to

produce a potent skin-preparatory toxin and the necrotizing activity in the rabbit's lung.

The experiments reported in following paragraphs represent an attempt to prove that the capacity of this particular anaerobe to produce a lung-preparatory toxin is correlated with the natural pathogenicity of the organism for the lung. For the lung-preparatory factor live virulent and avirulent cultures of this anaerobe were employed, also heat-killed cultures and culture filtrates. For the provocative factor (nonspecific), given intravenously, toxin of proved potency from homologous or from heterologous sources was employed. The description of the methods of preparing, titrating and administering homologous toxin (i. e., toxin produced by this organism) and heterologous toxin (typhoid toxin, meningococcus toxin) is beyond the scope of this paper; the reader is referred to the original publications.[12] Every toxin employed was tested for potency by means of the Shwartzman phenomenon in the rabbit's skin.

In preliminary experiments (series 1) 50 rabbits were inoculated intratracheally with a virulent culture of the necrophorus-like anaerobe, and 22 of these were set aside as controls. The remaining 28 rabbits received varying doses of toxin intravenously after twenty-four hours, followed in some cases by additional doses at twenty-four hour intervals. The inoculums were either twenty-four or forty-eight hour cultures and were given in doses of either 1 or 2 cc. intratracheally. The toxin was either homologous, given intravenously in doses of 2 to 10 cc. per kilogram of body weight, or heterologous (B. typhosus toxin), given in doses of 5 cc. per kilogram of body weight.

The results were as follows: Of the 28 rabbits receiving toxin intravenously, 24 presented lesions of the lungs at autopsy. No significant differences were noted whether 1 cc. or 2 cc. of inoculum had been given intratracheally, or whether homologous or heterologous toxin had been employed. The number of rabbits used was too small, however, to permit conclusions. Of the 22 rabbits that failed to receive toxin intravenously, 14 presented lesions at autopsy.

On the basis of incidence alone, the slightly higher number of positive results in animals receiving toxin did not appear to be decisive. A difference could be appreciated, however, in the appearance of the lesions. On gross inspection the lesions of the series receiving toxin appeared larger. Microscopically, they seemed to exhibit a greater intensity of leukocytic infiltration and of necrosis. In other respects the lesions in both series were identical.

The incidence of lesions in the control series (14 of 22 rabbits) was somewhat smaller than that in an earlier series (23 of 27 rabbits). This falling off of virulence suggested an attenuating effect of repeated subcultures in artificial mediums. The apparent restoration to maximum virulence on the intravenous injection of the toxin in the toxin series (24 of 28 rabbits) prompted Cohen to undertake a deliberate attenuation of this anaerobe in order to sharpen the contrast between the results with and without the intravenous injection of toxin.

12. Shwartzman.[3a] Cohen.[4]

The results of these and subsequent experiments are tabulated here:

	Rabbits Showing Pulmonary Lesions	Total Number of Rabbits
I. Intratracheal injection of attenuated microorganisms combined with intravenous injection of homologous or heterologous toxin (experiments of Dr. Cohen)		
A. Slight attenuation (simple subculturing)		
Controls (without toxin)	14	22
Rabbits that received toxin intravenously	24	28
(Lesions were more extensive grossly; histologically, they showed more leukocytes and necrosis, and the surrounding parenchyma, more fibrin and edema.)		
B. Moderate attenuation (repeated subculturing in artificial mediums, exposure to room temperature, cultivation in absence of blood, etc.)		
Controls (without toxin)	5	14
Rabbits that received toxin intravenously	9	15
(Lesions were of increased size, number and intensity.)		
C. Complete attenuation (exposure to room temperature for one month, subculturing in presence of homologous antiserum produced in dog, also subculturing in presence of bile.)		
Controls (without toxin)	0	45
Rabbits that received toxin intravenously	11	28
II. Intratracheal injection of heat-killed cultures		
Controls (without toxin)	0	7
Rabbits that received toxin intravenously	0	6
III. Intratracheal injection of culture filtrate		
Rabbits that received toxin intravenously	0	4

From these results it appears that the intravenous injection of toxin (homologous or heterologous) enhances the virulence of this anaerobe regardless of the degree of the latter's attenuation. With slightly attenuated cultures (group A) the virulence was fully restored. With completely attenuated cultures (group C) the restoration of virulence was decisive and marked, approaching that of moderately attenuated cultures (group B). Of significance, too, was the fact that the basic appearance of the lesions produced in these experiments, even with completely attenuated cultures, was the same as that of lesions caused by virulent cultures.

The results were rather striking, particularly those in which typical specific lesions were obtained with completely attenuated cultures and with heterologous toxin, and led to additional experiments. These were carried out (1941) in more or less the same form as those in group C, which was the crucial experiment.

This phase of the work was begun after an interval of nearly eight years, during which the anaerobe was carried in an unbroken series of subcultures in artificial mediums.

The biliary attenuation procedure employed in group C was selected because of its simplicity. The culture (previously tested for freedom from contamination) was transplanted into fresh Smith-Noguchi medium containing added sterile defibrinated rabbit blood and incubated for forty-eight hours. When vigorous growth and evolution of gas with a foul odor were not obtained in the first transplant, one or two additional serial subcultures were made in the same medium and with the same period of incubation. This insured cultures of high virulence as tested by intratracheal inoculation in rabbits.

The first step in attenuation consisted in transplantation into liver hormone medium.[12a] This culture was incubated for twenty-four hours, after which 1 cc. of sterile fresh ox bile was added to the medium and the tube set at room temperature for five days. Transplantation was then made into plain broth and the culture incubated for eight days. Either 2 cc. or 4 cc. of the inoculum was employed for intratracheal injection, and the further procedure followed the directions outlined previously.

For the intravenous injection a heterologous toxin was employed (B. typhosus filtrate) diluted 1:5, 1:10 or more, depending on the titer determined by previous testing in the rabbit's skin. The amount given was 1 cc. per kilogram in each rabbit, and in these experiments a single intravenous dose was given exactly twenty-four hours after the intratracheal inoculation of the culture.

The results were as follows: Thirteen of 23 rabbits receiving both injections showed lesions specific for the anaerobe. Seven other rabbits presented nonspecific patchy pneumonia with focal necrosis; 3 rabbits had no lesions. Of 14 controls receiving only the intratracheal injection, 11 had no lesions, and 3 presented nonspecific patchy pneumonia with focal necrosis. This condition was apparently caused by incidental spontaneous infection with Bacillus lepisepticus and similar flora.

It appeared, therefore, that the intravenously injected toxin not only restored some of the lost virulence of the anaerobic cultures but also enhanced the virulence of spontaneous infections.

The evolution of the toxin-produced lesion was also studied, beginning three hours after the toxin was introduced intravenously into animals that had received the attenuated cultures intratracheally twenty-four hours previously. As with virulent cultures, the early findings were scattered areas of dense atelectasis

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12a. Liver hormone medium is prepared from the following materials:

Fresh liver (veal or beef, free of fat)	1,307 Gm. (3 lb.)
Plain broth	4,500 cc.
Dextrose	45 Gm.
Tenth-normal sodium hydroxide (added after boiling)	45 cc.

Directions: To 3 pounds (1,307 Gm.) of fresh liver add 35 Gm. of dextrose and 3,500 cc. of plain broth. Allow the mixture to reach the boiling point. Boil slowly for fifteen minutes, stirring occasionally. Remove the liver and set aside for later use. Add the remaining 1,000 cc. of broth and 10 Gm. of dextrose. Filter through cotton into 2 Florence flasks until the broth is clear. Add 45 cc. of tenth-normal sodium hydroxide. Adjust p_H to 7.4. Slice the liver into cubes and insert into anaerobic tubes; pour broth over the liver; pour sterile petrolatum over the surface of the broth. Autoclave at 10 pounds (4.5 Kg.) for ten minutes.

together with some leukocytic exudation and beginning necrosis. Controls, not receiving toxin intravenously, also showed patchy atelectasis with leukocytic exudation but no necrosis. Necrobiotic changes were present in the alveolar phagocytes and leukocytes in animals which had received toxin intravenously. Necrosis of the alveoli was prominent, taking the form of acidophilic swelling and fragmentation of the ground substance. The cement substance of the capillaries appeared swollen and often fused in a smudge with the rest of the alveolar septum and with the swollen and partly desquamated alveolar epithelium. Some of the capillaries were abnormally dilated and in places were broken down, with resulting hemorrhage. For the most part, they appeared contracted and more or less bloodless.

Twenty-four hours after the injection of toxin these changes were somewhat more advanced. In forty-eight hours the ground substance of the alveolar septums presented marked acidophilic swelling and foamy, granular alteration, also the capillary endothelium, the alveolar epithelium and the leukocytic exudate in the lumen. Nuclear breakdown had begun, with diffusion of chromatin into the cytoplasm. The involved area was nearly bloodless because of the choking of the capillaries by the swelling of the ground substance and of the endothelium. Vague zonulation was evident.

Four days after the injection of toxin the typical appearance of the specific lesion was apparent, including the well defined zonulation and sharp demarcation observed in the lesion produced by virulent cultures.

Controls, which received only the intratracheal injection, showed no necrosis even after several days, despite increased infiltration of leukocytes in some animals.

The effect of concentration of attenuated bacteria on lung-preparatory potency was studied: Several tubes of attenuated culture were centrifuged and the supernatant fluid discarded. The pooled sediments in doses of 4 cc. were injected intratracheally into 23 rabbits. Fifteen of these twenty-four hours after inoculation received toxin intravenously. Seven of the latter died within a few hours after receiving the toxin; the remaining 8 were killed one to five days later. Two of the 8 controls were killed three hours after intratracheal inoculation in an attempt to recover the micro-organism by culture of the lungs. These rabbits were not examined. The remaining 6 were killed and autopsies made one to two days after inoculation.

The results may be summarized as follows: Pulmonary changes were found in all rabbits on which autopsies were made regardless of whether or not toxin had been given intravenously. The findings consisted in circumscribed patches of dense atelectatic consolidation, showing histologically slight, moderate or marked exudation of leukocytes and corresponding degrees of focal acidophilic necrosis. In 1 of the 15 rabbits that had received toxin intravenously a small area characteristic of the typical lesion was seen as well. Otherwise there was no significant difference between those receiving toxin and the controls.

From these findings the conclusion was drawn that the concentration procedure robbed the attenuated anaerobe almost entirely of its capacity to prepare lung tissue for the Shwartzman phenomenon, apparently as a result of overexposure to air. The dense atelectasis with leukocytic exudation and focal necrosis within early lesions was explained as evidence of massive lysis of bacteria with liberation of toxins. This assumption was strengthened by the greatly diminished incidence of pulmonary lesions in the animals killed last. The postmortem cultures

of the lungs of all the rabbits which had received these concentrated attenuated cultures proved negative.

It was concluded, therefore, that if attenuation is carried beyond a certain point, lung-preparatory potency may be entirely lost and, conversely, that only the bacterial cells which maintain their viability in the lung are capable of preparing it for the phenomenon. The importance of strict anaerobiosis is also made clear inasmuch as a great loss of viability is shown to take place after a short exposure to air.

COMMENT

The present study was undertaken as part of a larger plan to investigate the genesis of pulmonary abscess, employing in part strains of organisms isolated from typical cases of the disease in human beings. A more thorough identification of these strains and a further study of their relative frequency will become necessary in subsequent investigations having as their ultimate purpose the experimental production in laboratory animals of lesions resembling the various forms of the disease in man.

The phase of the work reported here concerns the cultural characteristics and pathogenicity for the lung of a gram-negative strictly anaerobic bacillus obtained from the pus of a putrid abscess in a human lung. Within the limitations of the present study, in which no special stress was laid on bacteriologic identification, the characteristics observed seemed to relate the organism to B. necrophorus. It produced a foul odor in various cultural mediums and was highly virulent for rabbits when injected in pure culture subcutaneously or intratracheally. It was also virulent for mice.

From the point of view of morphology the pulmonary lesion produced by the intratracheal injection of the bacillus was remarkable for its sharp demarcation, even in its earliest stages, and for the dense atelectasis, which formed the matrix for the other features of the lesion, viz., leukocytic exudation and necrosis. The infiltration of leukocytes was peculiarly dense at the margin of the lesion, where they, with the parenchyma, quickly underwent necrobiosis. The capillary blood channels in the marginal zone became obliterated early, and as a result the enclosed parenchyma (and pleura) presented simple ischemic necrosis. Eventually the necrotic areas became sequestered and liquefied so that the entire lesion became an abscess and often involved the pleural cavity to form an empyema.

Studies of the evolution of the specific lesion in successive stages yielded evidence that this strain of anaerobic bacilli survived only in those areas of the lung where intratracheal injection brought about the degree of atelectasis and circulatory blockage needed to produce an anaerobic environment. Consequently the lesion remained confined to the atelec-

tatic area of initial implantation and hence sharply demarcated. When the development of anaerobiosis was impeded as, for example, by repeated forced inhalation of a mixture of 95 per cent oxygen and 5 per cent carbon dioxide, the pathogenicity of the culture was diminished. Specific lesions were few and small and rarely reached the pleural surface. Often the only finding was patchy dense atelectasis with little or no acute inflammation or necrosis. The therapeutic application of this observation to the prophylaxis of anaerobic abscess of the lung in man is worthy of consideration, but the experiments described here were too few to have more than suggestive value.

The mechanism of necrotization in areas infected with this anaerobe remains the key question in a study of the pathogenicity of the organism. Cohen's views, embodied in part in this paper, stressed the Shwartzman phenomenon as the underlying principle in the necrosis of the lung, whether produced by the usual synergistic mixture or by a single species of organisms endowed with primary virulence. Although the classic Shwartzman phenomenon is described as extremely severe hemorrhagic necrosis, hemorrhage is not inevitably present, as shown in experiments in certain organs and tissues.[3b]

Cohen,[4] in his first approach to the analysis of putrid abscess of the lung through the Shwartzman phenomenon, demonstrated that pure cultures of the usual types of anaerobes recovered from human lungs thus involved not only failed on intratracheal injection to produce abscess of the lung in rabbits but were unable to produce in vitro toxins that were potent as skin-preparatory factors for the phenomenon. On the other hand, certain symbiotic mixtures of these anaerobes, grown together in vitro, yielded toxins possessing a considerable degree of skin-preparatory potency. Toxins with provocative potency were regularly found in the pure cultures.

Later work revealed in certain cases of pulmonary abscess a type of anaerobic bacilli which produced toxin with preparatory potency as well as provocative potency when grown in pure culture and which was capable, furthermore, of producing severe necrotizing lesions in the lungs of rabbits when injected intratracheally. The correlation thus found between preparatory potency and pathogenicity led to the assumption that the latter was dependent on the in vivo production by this particular type of toxic factors capable both of preparing tissue for the Shwartzman phenomenon and of provoking this phenomenon in the course of infection. These factors, in turn, were assumed to react synergistically, the preparatory factor sensitizing the tissue perivascularly, the provocative factor entering the blood stream to revert to the prepared site by the endovascular route, in accordance with the requirements for elicitation of the phenomenon.[3b]

Experimental proof of these assumptions was facilitated by the fact that in the production of the phenomenon the provocative factors bear

no intrinsic relation in kind or degree to the preparatory factors.[13] A micro-organism may produce considerable preparatory factor, yet relatively little provocative factor, and vice versa.

In the experiments now recorded it was demonstrated that the intravenous injection of either homologous or heterologous toxin twenty-four hours after intratracheal inoculation of attenuated cultures of this anaerobe results in necrotic lesions indistinguishable from the specific lesion produced by virulent cultures. Controls presented merely foci of dense atelectasis and mild leukocytic exudation.[14] The conclusion seems warranted that as a result of attenuation provocative potency is lost but preparatory potency is largely retained.

The question might be asked whether the focal atelectasis and the mild exudation of leukocytes seen in the lungs of controls are the visible representation of the preparation of the lung for the Shwartzman phenomenon. If so, might they not be nonspecific and reproducible by any micro-organism capable of evoking inflammation in the lung?

These questions can be answered by reference to the experiments with cultures which were killed by heat or weakened by excessive exposure to air, in which it was found that lung-preparatory potency was completely lost. In one experiment heavy intratracheal inoculation of air-weakened, attenuated cultures produced fairly extensive atelectasis and acute inflammation with multiple foci of necrosis, but the rabbits receiving toxin intravenously did not show significant effects of the added toxin as compared with controls. These lesions were attributed to irritant toxins liberated by bacteria undergoing lysis en masse. The relative failure of preparation of the lung on intratracheal injection of nonviable cultures or of culture filtrates must be laid to failure of interstitial (perivascular) union between toxin and tissue. On the other hand, the living organism, endowed with natural invasiveness even though attenuated, presumably achieves this in the course of implantation. Moreover, it appears that the degree of inflammation, atelectasis or other change produced by the anaerobe does not necessarily correspond with its tissue-preparatory potency. In all probability the latter alone is type specific, and after the implantation of the attenuated form the intravenous injection of any potent provocative factor results in a necrotic lesion typical of the virulent form.

An explanation of necrosis brought about by bacterial synergism, as in the ordinary case of putrid abscess of the lung, in which one finds a

13. Shwartzman,[3] chap. 2, p. 31.

14. A corresponding lack of local reaction was observed in each of 2 rabbits twenty-four hours after 0.25 cc. of a similarly prepared culture of the anaerobe had been injected intradermally. Four hours after these rabbits had been given typhoid toxin intravenously, the previously injected skin sites presented lesions typical of the Shwartzman phenomenon and having an intensity recorded as ++++.

mixture of several types of anaerobes that individually are nonpathogenic, is also supplied by these experimental results. The usual anaerobic bacilli of this group, although individually lacking in preparatory factors, are a rich source of provocative factor, as previously demonstrated.[5] The anaerobic streptococcus and the anaerobic diphtheroid which are found regularly in cases of putrid abscess of the lung may be suspected as the source of preparatory factor despite their apparent innocuousness. Proof of this is still lacking, and further work is contemplated along this line.

SUMMARY

Previous studies have demonstrated that pure cultures of the anaerobic micro-organisms recovered from the usual mixed flora of putrid abscess of the lung in man are incapable of reproducing the lesion in animal experiments. Exceptionally, certain anaerobic bacilli have been found which are pathogenic in pure culture. One such bacillus is described in the present report with special reference to the mechanism of its action when it is introduced intratracheally into the lung of a rabbit.

Culturally and otherwise it resembled B. necrophorus. From the point of view of morphology the lesion caused by it appeared to be specific. In the genesis of this lesion, studied in various stages, the primary incident was seen to be lobular atelectasis, which provided an anaerobic environment for the survival of the bacterium. Forced inhalation of a mixture of oxygen and carbon dioxide largely prevented the development of the lesion. Dense leukocytic infiltration and necrosis quickly followed the primary atelectasis and formed a sharply demarcated consolidation ending in abscess with or without empyema.

The factors in the production of necrosis by this anaerobe were studied by application of the principles of the Shwartzman phenomenon. Earlier experiments had shown that pure cultures of the usual anaerobic bacilli found in putrid abscess of the lung failed to produce potent skin-preparatory toxins for the phenomenon, although active in producing potent provocative toxins Conversely, the exceptional anaerobic bacilli which were pathogenic in pure culture were capable likewise of producing potent skin-preparatory toxins.

In the experiments reported here, the capacity to produce a necrotizing lesion in the lung of the rabbit was abolished by subculturing the anaerobe in the presence of bile. Nevertheless the capacity to produce potent skin-preparatory and lung-preparatory toxins endured, as proved by the production of necrotic lesions in prepared sites in the skin and the lungs, respectively, by injecting potent provocative toxins intravenously at a suitable interval, in accordance with the requirements for elicitation of the Shwartzman phenomenon. The lesions thereby produced in the lungs were identical with those produced in a primary manner by virulent cultures.

IMMATURE BOTRYOID TUMORS OF THE CERVIX

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In 1867 Weber [1] described the first of a series of uncommon and peculiar tumors of the cervix which subsequently received various names, such as "sarcoma botryoides," "myxochondrosarcoma," "myosarcoma striocellulare uteri," "mixed tumor" and "dysontogenetic tumor" (one type). Most of these tumors have been called sarcoma. In the present state of knowledge it might still be best to refer to them according to their gross appearance, as in the instance of sarcoma botryoides.[2] Yet this is not entirely satisfactory either, since there still remains the possibility that these growths are teratomatous, a likelihood that has not been generally entertained. Some of these immature, rapidly growing polypoid tumors, although grossly appearing alike, may be quite different histologically, some seeming to be pure sarcoma, containing round or spindle cells or both, while others in addition contain embryonal striated muscle and cartilage. These are the so-called mixed tumors or mixed mesodermal tumors. Furthermore, some tumors have been described containing these foreign histologic elements that grossly were not polypoid at all. McFarland [3] in an interesting paper discussed the dysontogenetic tumors. Only those growths showing a botryoid appearance are discussed in the present paper.

LOCATION AND AGE INCIDENCE

There are three possible places of origin: the corpus uteri, the cervix and the vagina. There is a definite difference in the average age at which the tumor is first seen, and in the number of cases reported from each of the three sites, although accurate statistics are not possible. The largest single group apparently arises from the vagina,[4] while there is a difference of opinion as to the numbers arising from the cervix and the corpus.[5]

1. Weber, O.: Virchows Arch. f. path. Anat. **39**:216, 1867.
2. Pfannenstiel, J.: Virchows Arch. f. path. Anat. **127**:305, 1892.
3. McFarland, J.: Surg., Gynec. & Obst. **61**:42, 1935.
4. McFarland, J.: Am. J. M. Sc. **141**:570, 1911.
5. Meikle, G. J.: J. Obst. & Gynaec. Brit. Emp. **43**:821, 1936. Shaw, W.: ibid. **35**:498, 1928.

TABLE 1.—*Immature Botryoid Tumors of the Cervix Containing Heterologous Tissue*

Author	Age	Description of Tumor	Metastases	Outcome
Weber [1]	45	From anterior lip of cervix. Spindle cells and embryonic striated muscle cells	Parametrium; uterine cavity	Death in 1 year; perforation of mass into peritoneum
Kunert [12]	35	From cervix. Large round cells and single strands of striated muscle fibers	Parametria; vault of vagina; 7th and 8th left ribs	Death in 1¾ years; cachexia
Thiede, M.: Ztschr. f. Geburtsh. u. Gynäk. **1**: 460, 1877	45	From cervix. Myxomatous and fibrous tissue; cartilage	.....	Death in 3 years; exhaustion
Rein [9b]	21	From anterior and posterior lips of cervix. Round, spindle and star-shaped cells; tissue myxomatous; cartilage	Left parametrium; vault of vagina; left pelvic lymph nodes	Death in 2 years; peritonitis; perforation of metastases into left parametrium
Müller, W.: Arch. f. Gynäk. **30**: 249, 1887	24	From cervix. Round and spindle cells; striped muscle	Left broad ligament; myxomatous tissue, cartilage	Death 1 year after operation; peritonitis
Pernice [8a]	17	From cervix. Myxomatous tissue; round and spindle cells, striated muscle; cartilage in recurrent tumor	Endometrium; free peritoneal part of pelvis, between symphysis and bladder	Death in 1½ years; cachexia, hypostatic pneumonia
Richter, cited by Peham, H.: Monatschr. f. Geburtsh. u. Gynäk. **18**: 191, 1903	2¼	From cervix. Round cells; myxomatous tissue; striated spindle cells	.....	Death after 2 years
Pfannenstiel [2]	53	From anterior wall of cervical canal. Round and spindle cells; hyaline cartilage	.....	Cachexia, recurrence of symptoms at last report
Pick, L.: Arch. f. Gynäk. **46**: 191, 1894	2½	From posterior wall of cervix. Large round cells; striated muscle	Extension to uterus	Death in 6 months; cachexia
Wilms [9]	41	From cervix. Round and spindle cells; cartilage; embryonic myxomatous tissue	Mesentery and parametrium	Death in 1½ years; perforation of uterus, peritonitis
Peham, H.: Monatschr. f. Geburtsh. u. Gynäk. **18**: 191, 1903	18	From cervix. Striated muscle; cartilage; myxomatous tissue	Pelvic peritoneum	Death 11 months after last operation; cachexia
Kehrer, E.: Monatschr. f. Geburtsh. u. Gynäk. **23**: 646, 1906	38	From right wall of cervix. Round and spindle cells; cartilage; bone; myxomatous tissue	.....	Death from intestinal obstruction
Michel, G., and Hoche, L.: Compt. rend. Soc. d'obst. de Paris **9**: 44, 1907	35	From cervix. Sarcoma with cartilage	.....	Unknown
Bäcker and Minnich [16]	25	From cervix. Spindle cells; cartilage	.....	Death in 7 years; cachexia; edema of lung
McCann, F. J.: J. Obst. & Gynaec. Brit. Emp. **14**: 202, 1908	52	From cervical canal. Immature cells; cartilage	.....	Unknown
Puech, R., and Massabaum, G.: J. méd. franç. **2**: 355, 1908	59	From cervix. Myxomatous tissue; cartilage; spindle cells; glandular tissue	.....	Well for 6 years. No further follow-up
Heddäus [14]	48	From cervix. Cartilage	Pleura	Death. See text
Cox, D. M., and Benischek, W. L.: Am. J. Obst. & Gynec. **16**: 28, 1928	29	From anterior lip of cervix. Bicornuate uterus, one side pregnant. Round and spindle cells; striated muscle, cartilage	.....	Death 1 year after onset
Beckmann, W.: Ztschr. f. Geburtsh. u. Gynäk. **75**: 586, 1914	22	From cervix. Round cells; cartilage; bone	Cavity of pelvis	Death 13½ months after being seen; debility
Meikle [5]	48	From anterior lip of cervix. Cartilage; spindle cells	.....	No recurrence 18 months after hysterectomy
Medina, J.: Rev. de gynec. d'obst. **31**: 3, 1937	35	From anterior lip of cervix. Striated muscle	.....	Unknown

TABLE 2.—*Immature Botryoid Tumors of Cervix Not Containing Heterologous Tissue*

Author	Age	Description of Tumor	Metastases	Outcome
Spiegelberg, O.: Arch. f. Gynäk. **14**: 178, 1879.....	17	From anterior lip of cervix. Spindle and round cells; hydropic intercellular substance	Corpus uteri; posterior wall of bladder	Death 1¾ years after onset; postoperative peritonitis
Spiegelberg, O.: Arch. f. Gynäk. **16**: 124, 1880.....	31	From posterior lip servix. Round cells; myxomatous-like tissue	Parametrium; between vagina and rectum; vaginal vault	Death in 1½ years; bowel obstruction and peritonitis
Winkler, F. M.: Arch. f. Gynäk. **21**: 309, 1883.....	47	From cervix. Large round and spindle cells; hydropic intercellular substance	Parametria; vaginal mucosa; endometrium	Death in 9 months; cachexia
Kunitz, E.: Ueber Papillome der Portio vaginalis uteri, Berlin, G. Schade, 1885	19	From cervix. Round and spindle cells; myxomatous tissue	Cervical canal; right parametrium	Not definite
Munde, P. F.: Am. J. Obst. **22**: 126, 1889.....	19	From cervix. Myxomatous tissue; glands	.....	Not given
Worrall, R.: Australasian M. Gaz. **15**: 292, 1896.....	23	From cervix. Myxosarcoma. No details	.....	Not given
Emmet, B. M.: Am. J. Obst. **45**: 386, 1902.....	19	From posterior lip of cervix. Spindle cells. No details	.....	Death in 1 year
Curtis, H. J.: Tr. Obst. Soc. London **45**: 320, 1904.....	1	Tumor filling vagina. Round and spindle cells; edematous tissue	Left iliac vessels embedded in growth	Death 2 days after operation
Phillips, J. E.: Virginia M. Semi-Monthly **9**: 508, 1904-1905	15	From cervix. Spindle cell sarcoma. No details	Whole pelvis filled to brim	Death 3 months after mass in pelvis appeared
Williamson, H.: Tr. Obst. Soc. London **47**: 119, 1906....	39	From anterior lip of cervix. Round and spindle cells	Parametria	Not given
Purslow, C. E.: Proc. Roy. Soc. Med. (Sect. Obst. & Gynaec.) **2**: 81, 1908-1909	21	From cervix. Giant cell sarcoma	Pelvis above pubis	Death 1 year after hysterectomy
Hellier, J. B.: J. Obst. & Gynaec. Brit. Emp. **26**: 108, 1914	34	From posterior lip of cervix. Spindle cells; myxomatous tissue	.....	Death in 2¾ years; cachexia
Reusch, W.: Zentralbl. f. Gynäk. **40**: 37, 1916.....	16	From posterior cervical wall. Spindle cells; myxomatous tissue	.....	Not given
Jones, S. W. M.: J. Obst. & Gynaec. Brit. Emp. **35**: 320, 1928	18	From cervix. Spindle and round cells; myxomatous tissue	Tumor to umbilicus	Death 1 year after onset
Cox, D. M., and Benischek, W. L.: Am. J. Obst. & Gynec. **16**: 28, 1928	21½ mo.	From cervix. Spindle and round cells; myxomatous tissue	Pelvis filled; hydronephrosis	Death 2 years after onset
Mátyás, M.: Zentralbl. f. Gynäk. **55**: 2739, 1931.....	25	From cervix. Spindle cells, sparsely cellular connective tissue. Patient had exophthalmic goiter	.....	Unknown

The tumors arising from the corpus tend to appear between 45 and 65 years of age,[6] while those of vaginal origin are mostly seen in infants and young children. The immature polypoid tumors of the cervix I have found described in the literature have been divided into those which arise from the cervix and contain heterologous elements and those in which the external appearance is the same but in which no heterologous tissue was reported. For the 22 cases in the former group the average age of incidence was 32 years, with a range of from 2¼ to 59 years. For the 16 cases in the latter group the average age was 22 years, with a range of from 1 year to 47 years. It is quite possible that many of the tumors in the second group really belong to the first, since the heterologous elements may easily be missed. The statement [2] that the majority of these cervical tumors occur in the age period under 20 years or in that following the menopause, with few in the intervening period, is not correct. Of the 22 cases in the first group, 12 were those of patients over 20 or under 46 years of age.

DESCRIPTION OF TUMORS

Classification is not easy. Cervical tumors are either diffuse or polypoid, although Ewing [7] has written that the latter represent a natural tendency of growth of the former and that there is no essential difference between them. McFarland [8] stated that the botryoid appearance results only from the amount of moisture the tumor happens to contain. Histologically, the chief distinction has been drawn between those tumors containing heterologous elements and those which are pure sarcoma. The gross classification seems the better one, for in the present state of knowledge it is simple and, further, the peculiar manner of growth deserves some emphasis.

Macroscopically, in the usual case the vagina is partially or completely filled with polypoid growths varying in size from that of a pea to that of a plum, whose origin by a narrow pedicle can be traced to one or the other lip of the cervix or to the canal. Such polyps may even be found protruding from the vulva. They are easily broken off, and the examining hand may come away holding several of them. There is much resemblance to a hydatidiform mole. The polyps are pinkish gray and look cystic, but if cut across they are found to be solid or semisolid and of a rather gelatinous consistency. They apparently arise in the subepithelial layers of the cervix.

6. Liebow, A. A., and Tennant, R.: Am. J. Path. **17**:1, 1941.

7. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1940, pp. 287-292.

Microscopically, there are two types to describe. Those of simpler composition consist in the main of spindle and round cells, one type usually predominating, while the presence of giant cells is not uncom-

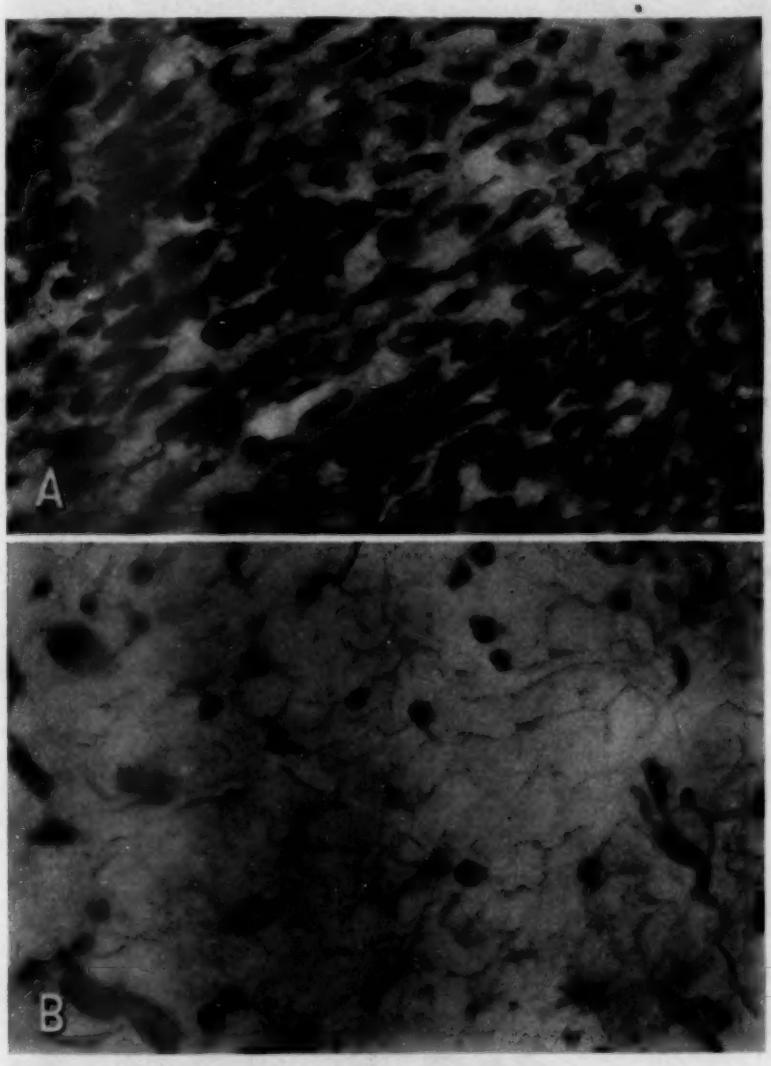

Fig. 1.—*A*, immature cells tending toward spindle formation in one portion of the tumor. Hematoxylin and eosin stain; × 500. *B*, myxomatous-like tissue, showing paucity of cells. Hematoxylin and eosin stain; × 500.

mon. A goodly portion of the tumor is occupied, however, by areas containing much intercellular substance and few cells. The nature of this portion of the growth has been the subject of much controversy.

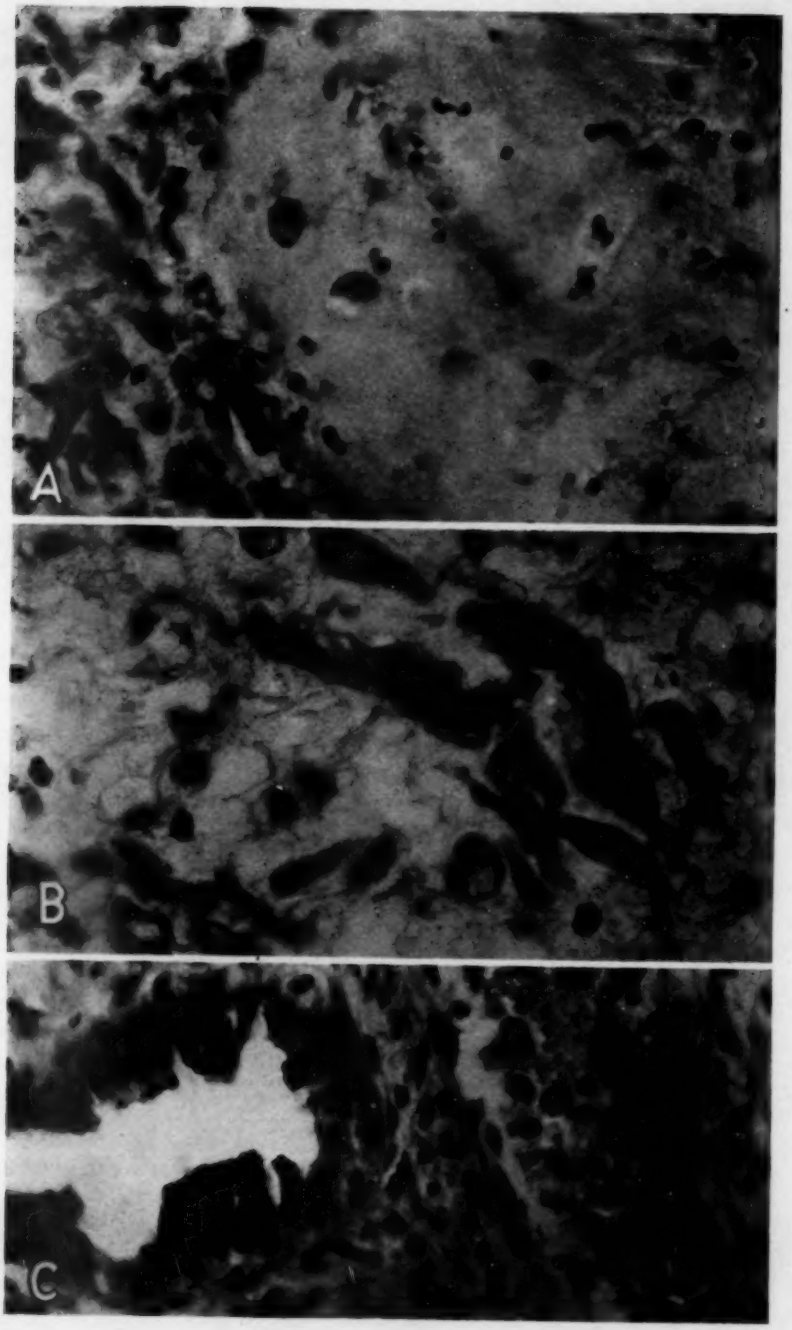

Figure 2

(See legend on opposite page)

Some consider it true myxoma.[8] Wilms [9] considered it to be embryonic mesenchymal tissue, believing this to be the fundamental constituent of the tumor, from which the other tissues are derived. Should this be true, then separation of these tumors into two groups would be quite artificial, and those listed in table 2 would represent tissue not yet showing heterologous elements but which later on might do so. Pfannenstiel [2] and Spiegelberg [10] considered that edema alone caused the appearance of this tissue. The latter based his opinion on the negative reaction for a test for mucin ("sarcoma lymphangiectaticum et hydropicum"). Whatever the exact nature of this tissue, the appearance is quite characteristic. The cell bodies are more or less star shaped or triangular with long protoplasmic threads, producing a loose network. The intercellular substance is abundant, clear or somewhat granular, sometimes eosinophilic. The cell nuclei are round or oval.

Those tumors containing heterologous elements show areas exactly as just described, with the addition here and there of patches of either islands of cartilage or strands of striated muscle cells or both, although the latter may be difficult to find. Striated muscle was noted in 10, and hyaline cartilage in 17, of the 22 cases. Both striated muscle and cartilage occurred in 5 of these cases.

Osteoid tissue is rare, having been described in only 2 cases of botryoid tumor. These tumors are vascular. One of the unusual features is the completeness of the epithelial covering, which is usually squamous epithelium. Care must be taken in examining the most superficial polyps, which may resemble a mature tumor.

The question of the presence of glandular elements is an important one. It is the consensus that these are inclusions. However, some of the acini in the sections in the case now described appear to have actively proliferating cells with heavily chromatic nuclei, but not as yet

8. (*a*) Pernice, L.: Virchows Arch. f. path. Anat. **113**:46, 1888. (*b*) Rein, G.: Arch. f. Gynäk. **15**:187, 1880.

9. Wilms, M.: Die Mischgeschwülste der Vagina und der Cervix uteri, Leipzig, A. Georgi, 1900.

10. Spiegelberg, O.: Arch. f. Gynäk. **4**:344, 1872.

EXPLANATION OF FIGURE 2

A, very early cartilage formation. This appears more clearly under the microscope than in the photograph. Hematoxylin and eosin stain; × 500.

B, embryonic striated muscle cells with cross striations especially evident. The tumor showed many such cells, some closely, others more loosely packed. Hematoxylin and eosin stain; × 700.

C, small cervical gland. Note heaped-up, irregular epithelium. See text for discussion of glandular elements. Hematoxylin and eosin stain; × 500.

truly anaplastic cells. If these glandular elements are an essential part of the tumor, it should be classified as teratoma. On the other hand, it may be that these glandular elements are stimulated to proliferation by what von Hansemann has termed "collateral hyperplasia." This change has been described as occurring in either the gland cells or the stroma of the invaded tissues and occasionally is scarcely distinguishable from neoplasia, there being perhaps some sort of trophic action on these adjacent tissues by the tumor.

Cases have been described in which there was present just one polyp, containing striated muscle or cartilage or both.[11] This may represent the early stage of the botryoid appearance.

HISTOGENESIS

The earliest considered possibility was that of metaplasia.[2] Some have described the transition of spindle cells to cartilage.[12] It is doubtful, however, if the transition between smooth and striated muscle has ever been proved.

Cohnheim's cell rest theory has been advocated, the tumor being traced to misplaced embryonal cells. Cohnheim considered that the cells originally belong to the wolffian body, but his explanation is inadequate since striated muscle is foreign to the wolffian system.

Wilms's modification of Cohnheim's theory has drawn the largest number of followers. In short, he supposed not that single cells but that undifferentiated embryonal germ tissues are split off from the region behind the renal anlage and carried toward the cloaca by the growth of the wolffian duct. He assumed, then, a common mother tissue from which cartilage as well as striated muscle may commence to grow. Of the factors that cause the growth, nothing is known. Parity plays no role in the causation of this tumor. It may well be that, as Oertel wrote in regard to another matter, "The sarcomatous . . . *manner of growth* is an expression of the conditions and environmental influences of the growth, rather than of cell derivation and character."

METASTASES AND EXTENSION

Distant metastasis is uncommon, while local recurrence and extension are the rule. The growth is commonly found to extend into the parametria, the broad ligaments, the pelvic peritoneum and the vagina. Death commonly results from pressure on the ureters by the tumor with hydronephrosis.

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11. Amolsch, A. L.: Am. J. Cancer **37**:435, 1939. Seydel, O.: Ztschr. f. Geburtsh. u. Gynäk. **45**:237, 1901. Spuler, R.: Centralbl. f. allg. Path. u. path. Anat. **16**:337, 1905.

12 Perlstein, I.: Surg., Gynec. & Obst. **28**:43, 1919.

Kunert [13] has reported metastases in the ribs. Perhaps the most interesting case is that recorded by Heddäus.[14] The patient was well for one and a half years after the primary tumor had been removed by vaginal hysterectomy. Then cough and right-sided thoracic pain developed, and later resection of a rib revealed 2 to 3 liters of hemorrhagic exudate and a tumor like a hydatid mole. The tumor appeared to spring from the diaphragmatic portion of the pleura. The patient died twenty-eight days later. Microscopically, the tissue resembled the primary tumor and contained many islands of cartilage. This case sheds light on the peculiar manner of growth of this tumor, in which apparently a free cavity is necessary for the development of the polypoid character, as in the vagina or the pleural cavity. Elsewhere, where no cavity exists, the tumor is solid.

CLINICAL FEATURES

It is possible to have extensive development of the tumor without any symptoms, even to the protrusion of the growth from the vulva. Usually, however, attention is drawn to the fact that something harmful is afoot by a watery, serosanguineous, mucoid or bloody discharge. Sooner or later this will acquire a foul odor. At times the patient will notice the passage of one or several polypoid masses, which she may insist are blood clots.

Pain is an indication that irremediable growth and damage have occurred. In the later stages vesical irritability and rectal tenesmus are common. As a later development, pressure on the ureters may cause hydronephrosis. Cachexia, anemia, a negative fluid balance and all the other evidences of declining metabolism inevitably ensue.

Physical findings will depend on the stage at which the patient presents herself, commonly enough about six months after the onset of any symptom, at which time the disease will be found to be already advanced. The appearance of the tumor has been described.

The diagnosis is made on microscopic study. Care is necessary, for important elements may be overlooked. At the Mayo Clinic [15] the chances of finding an immature growth in a cervical polyp are about 300:1. Even then the tumor is far more likely to be carcinoma.

The disease is invariably fatal. I know of no authenticated case of recovery. Ordinarily death occurs between one and two years after onset. The case of Bäcker and Minnich [16] is quite unusual in that the patient survived for seven years.

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13. Kunert, E.: Arch. f. Gynäk. **6**:111, 1874.
14. Heddäus, A.: Arch. f. klin. Chir. **94**:117, 1911.
15. Day, L. A.: Proc. Staff Meet., Mayo Clin. **14**:650, 1939.
16. Bäcker, J., and Minnich, K.: Beitr. z. Geburtsh. u. Gynäk. **10**:532, 1906.

Even wide surgical excision of the entire genital tract, with radiotherapy added, has yet to cure a patient. Unfortunately, no patient in an early stage has been treated surgically or by radiotherapy, hence no statement can be made as to the curability of the tumor in its early stages.

REPORT OF A CASE

A 14 year old white girl was admitted to the Sacramento County Hospital, Sacramento, Calif., Jan. 19, 1940, complaining of a yellowish, bloody vaginal discharge which had been present for six months. The menses had not been affected and occurred every twenty-eight days. The discharge was usually increased after the period. Three weeks prior to admission she passed what she called blood clots. There had been no pain or burning or any other complaint, the patient always having been robust and athletic.

Her parents were living and well; there were no siblings; there was no history of familial disease except carcinoma. The paternal great grandmother died of carcinoma of the breast; both grandmothers died of carcinoma of the stomach.

She was an obese girl, weighing 170 pounds (77 Kg.). She appeared of the stated age and was both alert and cooperative. Whereas elsewhere nothing of note was found, the small vaginal introitus showed multiple protruding grapelike bodies, many of them loose, and free oozing of blood. The entire cervix seemed to have been destroyed with what appeared to be an infiltrating neoplasm. Only after much difficulty was the cervical canal found. Routine laboratory tests, including a negative Aschheim-Zondek test, were noncontributory. The grapelike objects were found solid, of jelly-like consistency and grayish, hyaline in appearance. Dr. J. H. Schaefer reported that the polypoid bodies cut smoothly, leaving a clear firm surface with some submucous hemorrhage. The more superficial polyps showed myxomatous tissue covered with a single layer of squamous epithelium. Although some areas looked quite cellular, the tissue appeared to be essentially that of a mature fibrous polyp. The true nature of the growth became evident, however, on study of tissue taken from the cervix. This tissue was also examined by Dr. Stuart Lippincott,[17] of the National Cancer Institute, and in summary, the tumor revealed highly cellular areas of round and spindle cells, mesenchymal stroma separated by both edema and myxomatous tissue, and striated muscle cells. In addition, and of considerable importance, was the presence of acini, some of which appeared to have actively proliferating cells with heavily chromatic nuclei but which as yet were not truly anaplastic. It was Dr. Lippincott's opinion that the growth was teratoma.

The patient received 1,800 milligram hours of radium, and roentgen therapy was commenced. Six months later (June 1940) there was no local evidence of the tumor, but a hard mass filling the lower half of the abdomen had appeared and the patient had lost some weight. No pulmonary metastases were seen on roentgen examination. Further roentgen therapy caused good regression of the abdominal mass. By September 1940, the vagina was filled with necrotic tumor tissue, with complete infiltration of the right broad ligament, and the vaginal wall was invaded. In November 1940, after the removal of many small jelly-like masses, further tissue was obtained from the cervix. This tissue was grayish white and about the consistency of brain tissue. Part appeared gelatinous. Microscopically there were seen spindle cells in solid masses with clear cytoplasm

17. Lippincott, S. W.: Personal communication to the author.

and vesicular nuclei. There were frequent irregular mitotic figures. There was great vascularity, and in some areas there was a tendency to the formation of giant cells. There was one small area of early cartilage formation, with a hyaline background and a few cartilage cells.

The patient rapidly declined and died on Dec. 22, 1940, approximately one and a half years after the onset of symptoms. Permission for an autopsy was not obtained.

SUMMARY

The nomenclature used for the gross specimen should be employed in designating this tumor pending more exact classification, for there is much yet unknown about the tumor. Pathologists simply do not know why cartilage or striated muscle should appear in the cervix, and the phenomena outlined by Wilms, although attractive, have never been actually demonstrated. The possibility that this type of growth is teratomatous should be kept in mind. The polypoid character appears to depend on the presence of a free cavity, such as the vagina or the pleural cavity. Although no age is exempt, the majority of cases appear between puberty and the menopause. The prognosis is unfavorable.

PATHOLOGIC CHANGES IN THE LIVER AND KIDNEYS OF GUINEA PIGS DEFICIENT IN VITAMIN C

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AND
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During the course of an experiment in which trypan blue was injected into scorbutic guinea pigs, routine sections of kidney and liver were observed to contain greater amounts of the dye than similarly prepared sections from the control animals. This observation was so constant and striking in over 15 animals that another experiment more adequately controlled for this particular finding was undertaken. The following communication reports the results of the latter experiment.

METHODS

Scurvy was produced in the guinea pigs by feeding a ration known as rabbit chow checkers.[1] When guinea pigs are fed this diet exclusively, characteristic signs of scurvy develop, and the animals die in from twenty-one to twenty-five days. A group of control animals were fed the same diet and, as a source of vitamin C, given lettuce ad libitum. The inanition effect produced by the scurvy was controlled by a second control group of animals, which were given lettuce ad libitum but no rabbit chow, the animals being selectively starved so that they lost the same amount of weight as those receiving the diet deficient in vitamin C. That the disease produced by feeding the rabbit chow checkers was due entirely to the lack of vitamin C was demonstrated by placing a group of young growing guinea pigs (150 Gm.) on this diet and giving them daily intraperitoneal injections of ascorbic acid. The animals so treated maintained normal growth curves and showed none of the signs of vitamin C deficiency noted in the other animals. Several young guinea pigs were included in the experiment to see if age was a factor in the problem. The trypan blue was given subcutaneously in the flank of the animal in a 1 per cent concentration in physiologic solution of sodium chloride. The first injection of the dye was given on the fourteenth day of the experiment, for at this time the animals on the C-deficient diets began to show the first symptoms of scurvy. The amount of the dye given in each instance was

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1. The rabbit chow checkers are prepared and sold by the Purina Mills Company, of St. Louis. The rabbit chow is made from soy bean oil meal, wheat germ, corn germ meal, alfalfa meal, ground oats, corn meal, gray wheat middlings,

(Footnote continued on next page)

determined by the size of the animal. The adult guinea pigs, weighing from 400 to 600 Gm., were given 50 mg. of the dye on alternate days until a total of 200 mg. was reached. Only 80 mg. of the dye was given to the young guinea pigs weighing from 150 to 200 Gm. All of the animals in a group, with the corresponding control animals, were killed after the first spontaneous death occurred in a scorbutic animal of that group. This period varied from one to four days following the last injection of the trypan blue. Blocks of liver, spleen, kidney, adrenal gland, lung, intestine and heart muscle were fixed in a 3 per cent solution of formaldehyde, and paraffin sections were prepared and stained lightly with trinitrophenol (picric acid). The trypan blue was well preserved with this type of fixation and staining, and was easily seen in the sections.

RESULTS

The sections of liver and kidney from the scorbutic animals contained remarkably more trypan blue than the sections from the corresponding control animals. There was no significant difference in the amount of the dye deposited in the other organs examined. The livers of the scorbutic guinea pigs showed moderate to advanced fatty degeneration of the liver cells, particularly in the region of the central veins. The vacuolation of the liver cells was definitely identified as a fat by staining frozen sections of liver with sudan III. This fatty change was so constant and characteristic that in sections stained with hematoxylin and eosin those from the C-deficient animals were easily selected from among those representing the control animals. The dye was observed as minute granules indiscriminately placed throughout the cytoplasm of the liver cells, and the cells showing the fatty change stored the greatest amount of dye (fig. 1). In the livers from

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molasses, calcium carbonate, iodized salt, and riboflavine concentrate. The exact percentage of each constituent is secret and is not available. The mixture is pressed into small pellets.

Chemical analysis of rabbit chow checkers shows that their composition is as follows:

Protein	17.50 per cent
Fat	3.60 per cent
Fiber	15.00 per cent
Ash	6.00 per cent
Nitrogen free extract	47.00 per cent
Moisture	10.00 per cent
Calcium	1.10 per cent
Phosphorus	0.42 per cent
Magnesium	0.18 per cent
Potassium	0.90 per cent
Soluble chloride as Na Cl	0.90 per cent
Iron	2.75 parts per million
Copper	12.00 parts per million
Cobalt	0.05 parts per million
Manganese	100.00 parts per million
Carotene	3.00 parts per million
Vitamin D	2 U. S. P. units per gram.
Ascorbic acid	0.00 parts per million

The laboratory department of the Purina Mills Company has been unable to identify any ascorbic acid by chemical analysis.

the control animals only a rare granule of dye could be found within the liver cells. The Kupffer cells were filled with the dye both in the scorbutic and in the control animals.

The dye was observed in the cytoplasm of the cells of the proximal convoluted tubules of the kidneys in large granular masses. All of the animals showed significant amounts of the dye, with the scorbutic animals containing unmistakably larger amounts (fig. 2). In the scorbutic animals the dye in many instances so heavily infiltrated a cell that the outline of the nucleus was completely obliterated. Only occasionally did some of the cells of the excretory tubules contain a small amount of dye. No morphologic change was observed in the kidneys to account

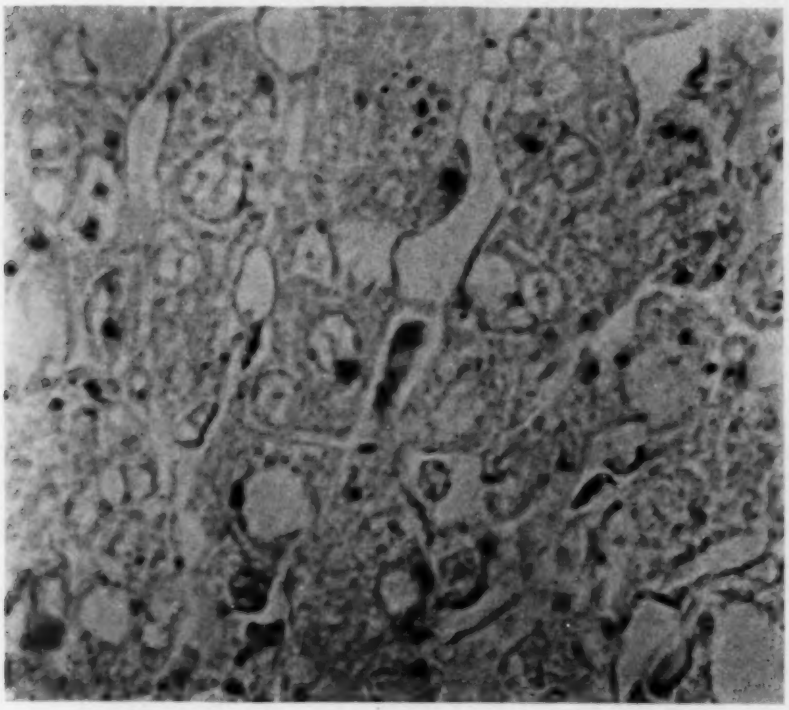

Fig. 1 (C-deficient animal 4).—Section of liver showing the trypan blue as fine black dots within the cytoplasm of the liver cells. Two Kupffer cells, plainly visible in the upper central part of the field, also contain granules of the dye. Note the large vacuoles of fat in the liver cells. Paraffin section with a light trinitrophenol stain; × 2,200.

for the increased storage of dye in sections stained with hematoxylin and eosin. Frozen sections of the kidneys stained for fat with sudan III showed no difference in the amount of fat in the deficient and in the control animals. The individual results for the animals in the several groups are recorded in tables 1 and 2. In estimating the amount of dye deposited or the degree of fatty metamorphosis in the liver cells a system of pluses was used. Four pluses indicate the maximal amount of dye or fat observed in any section.

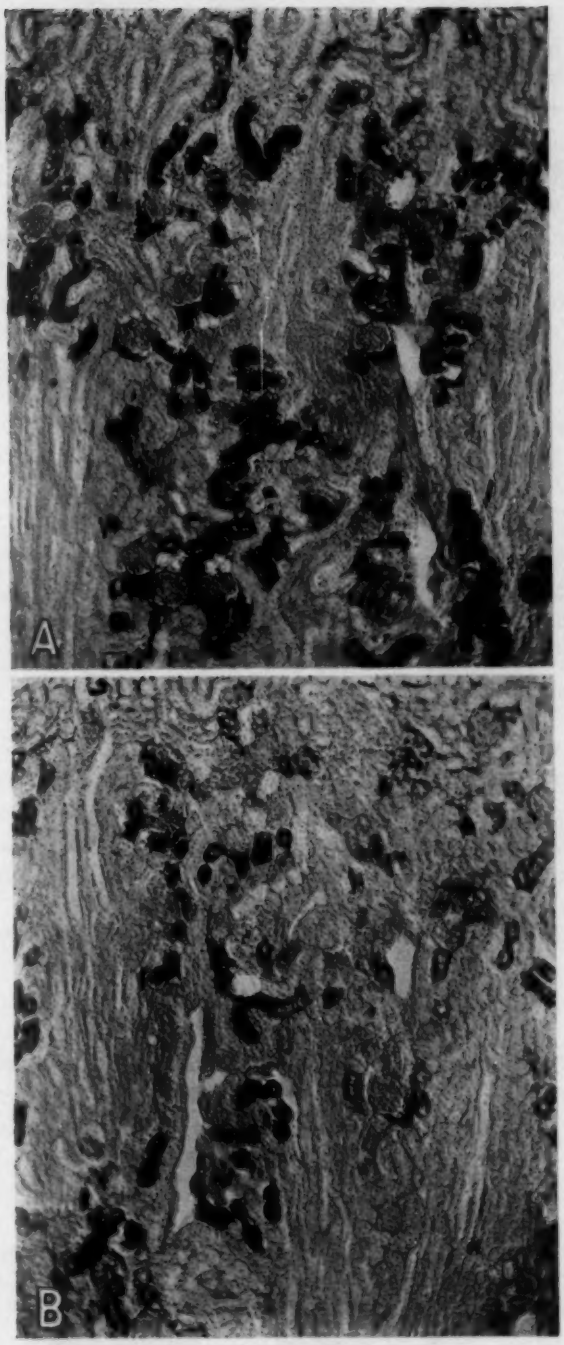

Fig. 2.—*A* (C-deficient animal 5), section of renal cortex showing large granular masses of trypan blue in the cells of the proximal convoluted tubules, completely obliterating all cellular detail. Paraffin section stained lightly with trinitrophenol; × 50. *B* (control animal 5), section of renal cortex showing slight amounts of trypan blue in the cells of the proximal convoluted tubules. Compare with *A*. *A* and *B* were photographed and processed under identical conditions. Paraffin section stained lightly with trinitrophenol; × 50.

TABLE 1.—*Trypan Blue Deposited in the Liver*

	Guinea Pigs Deficient in Vitamin C				Control Animals			
Animal	Weight, Gm.	Dose of Dye, Mg.	Amount of Dye Deposited	Fatty Metamorphosis	Weight of Animal, Gm.	Amount of Dye, Mg.	Amount of Dye Deposited	Fatty Metamorphosis
1	500	200	++++	+++	*508	200	+	+
2	544	200	+++	++++	*527	200	++	0
3	600	200	+++	++	*529	200	+	0
4	501	200	++++	++++	*600	200	+	+
5	568	200	++++	+++	*601	200	+	+
6	540	200	++	++	*552	200	0	+
7	618	200	+++	+++	*588	200	+	0
8	486	200	+++	++	*550	200	+	+
9	590	200	++++	++++	*612	200	+	+
10	525	Died after 1st injection of dye			*557	200	+	0
11	517	Died on 10th day—probably not vitamin C deficiency			*481	200	+	0
12	140	80	+	++++	*203	80	0	0
13	150	80	+	+++	*285	80	0	0
14	296	200	+++	++++	†427	200	+	++
15	377	200	+++	+++	†470	200	+	++
16	146	80	++	+++	†288	80	+	+
17	510	200	++++	++++	†384	200	+	+
18	555	200	+++	++	†397	200	++	+
19	568	200	++++	++++	†382	200	+	+
20	478	Died after 1st injection of dye			†518	200	+	++

* Received normal control diet.
† Received inanition control diet.

TABLE 2.—*Trypan Blue Deposited in the Kidneys*

	Guinea Pigs Deficient in Vitamin C			Control Animals		
Animal	Weight, Gm.	Dose of Dye, Mg.	Amount of Dye Deposited	Weight of Animal, Gm.	Amount of Dye, Mg.	Amount of Dye Deposited
1	500	200	++++	*508	200	++
2	544	200	+++	*527	200	++
3	600	200	++++	*529	200	+
4	501	200	+++	*600	200	+
5	568	200	++++	*601	200	+
6	540	200	+++	*552	200	++
7	618	200	++++	*588	200	+
8	486	200	++	*550	200	++
9	590	200	+++	*612	200	+
10	525	Died after 1st injection		*557	200	++
11	517	Died on 10th day—probably not vitamin C deficiency		*481	200	++
12	140	80	++	*203	80	+
13	150	80	++	*285	80	+
14	296	200	+++	†427	200	+
15	377	200	++++	†470	200	+
16	146	80	++	†288	80	+
17	510	200	++++	†384	200	+
18	555	200	++++	†397	200	++
19	568	200	++++	†382	200	+
20	478	Died after 1st injection		†518	200	+

* Received normal control diet.
† Received inanition control diet.

COMMENT

Because trypan blue has a strong affinity for all pathologically altered cells and dead tissue it appears that the results of our experiment indicate that vitamin C deficiency produces a pathologic change in the cells of the liver and the kidneys of the guinea pig. Since examination of the kidneys from the deficient animals failed to demonstrate any morphologic change, it can only be assumed that the cells of the proximal convoluted tubules where the dye was so heavily deposited were in some way physiologically altered. Further investigation will be needed to understand fully the significance of this isolated fact concerning the kidney in vitamin C deficiency because none of the known effects of vitamin C deficiency to our knowledge is in any way dependent on an altered physiologic function of the kidney.

Aschoff and Koch [2] described advanced fatty degeneration of the liver cells in human cases of scurvy and regarded the change as characteristic of that disease. This observation cannot be regarded as conclusive evidence that vitamin C deficiency in man produces fatty degeneration of the liver, because a spontaneously occurring deficiency disease is usually accompanied by other dietary deficiencies. However, Bessey, Menten and King [3] have showed that a deficiency of vitamin C will produce fatty metamorphosis of the liver in guinea pigs, and our experiment confirms this observation. The fatty change plus the fact that the liver cells in the C-deficient animals contained more trypan blue is good evidence that the vitamin C deficiency had produced a pathologic change in that organ. These findings are particularly interesting in the light of the recent work of Sealock and Silberstein [4] demonstrating that alkaptonuria follows the administration of l-tyrosine to guinea pigs. The severity of the alkaptonuria was observed to be closely correlated with the amount of vitamin C given the animals. Subsequent withdrawal of this vitamin resulted in the reappearance of the homogentisic acid commensurate with the degree of withdrawal. Further evidence that vitamin C is concerned with the metabolism of the aromatic amino acids has been reported by Levine, Gordon and Marples.[5] These investigators observed a spontaneous defect in the metabolism of aromatic amino acids in infants fed cow's milk containing 5 Gm. or more of protein per day. The defect was manifest in the excretion in the urine of l-p-hydroxyphenylacetic acid and p-hydroxyphenylpyruvic acids.

2. Aschoff, L., and Koch, W.: Skorbut, eine pathologisch-anatomische Studie, Jena, Gustav Fisher, 1919, p. 51.

3. Bessey, O. A.; Menten, M. L., and King, C. G.: Proc. Soc. Exper. Biol. & Med. **31**:455, 1933.

4. Sealock, R. R., and Silberstein, H. E.: Science **90**:517, 1939.

5. Levine, S. Z.; Gordon, H. H., and Marples, E.: J. Clin. Investigation **20**:209, 1941.

The administration of ascorbic acid completely eradicated this defect while other vitamin principles were ineffectual. These observations seem to offer good presumptive evidence that vitamin C is concerned with the catabolism of the aromatic amino acids. Since the liver is believed to play an important part in the metabolism of amino acids, the pathologic change in the liver cells as shown in our experiments is morphologic evidence in support of this idea.

SUMMARY

Trypan blue injected subcutaneously into scorbutic guinea pigs is more heavily deposited in the parenchymal cells of the liver and in the proximal convoluted tubules of the kidney than in the corresponding cells in control animals receiving the same amount of dye. This observation is interpreted as indicating a pathologic change in these cells as a result of the vitamin C deficiency. In the livers of the scorbutic animals there was a fatty metamorphosis of the liver cells, but no morphologic change was observed in the kidneys to account for the increased deposition of the dye. The morphologic change plus the pathologic deposit of trypan blue in the liver is regarded as evidence of hepatic damage from vitamin C deficiency and as a plausible explanation for the altered aromatic amino acid metabolism accompanying vitamin C deficiency which has been reported by other investigators.

FIBROUS PLEURAL ADHESIONS

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ST. LOUIS

Fibrous pleural adhesions have been seen so frequently by pathologists that they have occasioned attention only when associated with some obviously causal condition. Previous discussions of pleural adhesions have been concerned with the relation of the lesions to some specific disease or to some definite therapeutic problem. The purpose of this report is to present statistical information regarding the incidence of fibrous pleural adhesions and to analyze the data in terms of possible etiologic agents and factors.

METHODS

The material for this study was obtained at 400 unselected autopsies on persons whose ages ranged from 1 to 89 years. All these persons were from the population of general hospitals except 66, whose deaths were either traumatic or unexpected. Each specimen was studied without the aid of roentgenograms for anatomic lesions possibly related to fibrous adhesions of the pleura. Microscopic sections of representative adhesions were prepared in approximately one fourth of the cases. Sections of uninvolved pleura were prepared and studied as controls. The microscopic sections were stained with hematoxylin and eosin and by Verhoeff's method for the demonstration of elastic tissue.

GENERAL INCIDENCE

Of the 400 unselected cases studied at autopsy there were fibrous pleural adhesions in 264, or 66 per cent. It was evident that the incidence of adhesions increased with increasing age. Adhesions were rare in children, but were present in 79 per cent of persons aged 50 (chart). There were no adhesions of the pleura in 50 newly born infants observed at autopsy in this department but not included in this series. With regard to the persons less than 20 years of age, the apparent causes of the adhesions were found at autopsy in isolated instances. The associated causal conditions included unresolved pneumonia, bronchiectasis, abscesses of the lungs, empyema and rheumatic fever. In older persons the causes were usually not apparent.

INCIDENCE IN RELATION TO PARTICULAR CONDITIONS

Past Pneumonia.—The frequent association of pneumonia and fibrous pleural adhesions in younger persons suggested a causal rela-

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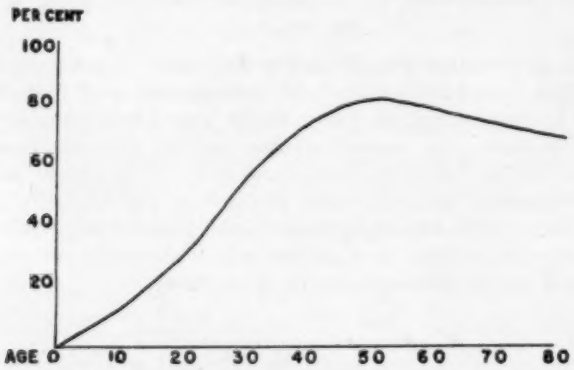
tion. Past histories of pneumonia or pleurisy or both were obtained from the charts of 49 patients. Forty-six of these patients, or 94 per cent, showed fibrous adhesions of the pleura at autopsy. This figure was significantly high, and all ages were represented in the group.

Calcified Nodules and Apical Scars.—The entire series was divided into five groups (table 1).

The first group, 97 patients, had no history of pneumonia and had no evidence of tuberculosis or other chronic inflammation. Only 50, or 52 per cent, showed fibrous pleural adhesions.

In the second group were 125 whose lungs contained calcified nodules. The nodules were interpreted as latent lesions of the first infection type of tuberculosis. There were no lesions of the reinfection type. Seventy specimens, or 56 per cent, showed adhesions which only occasionally were in the vicinity of a calcified nodule.



Percentage incidence of fibrous pleural adhesions at various ages as determined on specimens obtained post mortem from 400 persons.

TABLE 1.—*Incidence of Fibrous Pleural Adhesions*

Group	Patients	Average Age	Incidence of Adhesions, %*
No pneumonia and no tuberculosis	97	41	52
Calcified pulmonary nodules	125	47	56
Apical scars	125	59	81
Past pneumonia or pleurisy or both	49	50	94
Chronic pulmonary inflammation	4	..	100

* The incidence increases with the average age of the group and is not necessarily related to the lesions.

The third group included 125 patients from whom specimens were obtained having one or two apical scars in addition to calcified nodules. The apical scars were considered to be latent lesions of the reinfection type of tuberculosis. In 101, or 81 per cent, of these the pleura showed fibrous adhesions, a few of which were located over the scars.

The fourth group consisted of 49 patients with a past history of pneumonia or pleurisy or both. Ninety-four per cent showed adhesions.

The fifth group included 4 patients whose lungs presented chronic inflammation; one pair of lungs showed advanced tuberculosis, and three pairs showed advanced bronchiectasis. The adhesions were obviously related to the areas of inflammation.

The high incidence of fibrous pleural adhesions in the last two groups was significant. In the first three groups the incidence appeared to be increased in those with tuberculous lesions of the first infection and reinfection types. However, analysis showed that the incidence of pleural adhesions in the first three groups (table) increased with the average ages of the groups. Therefore, these figures showed no relation between latent tuberculosis and fibrous pleural adhesions.

Apical Scars and Apical Adhesions.—The pleura over apical scars was not the commonest site for the localization of fibrous pleural adhesions. In 125 lungs, totaling 250 apexes, there were 209 apical scars. Adhesions were associated with 33 of the 209 scars, or 16 per cent. Conversely, there were adhesions over 79 of the 800 apexes in 400 pairs of lungs. Beneath 27 of the 79 adhesions there were apical scars. From these figures it is evident that about 1 apical scar in 6 had an overlying adhesion and that only 1 apical adhesion in 3 was associated with an apical scar.

AREA OF PLEURA INVOLVED

In each of the 400 specimens the area of pleura covered by adhesions was estimated. Forty-six persons with a history of pneumonia or pleurisy or both showed an average area of involvement of 23 per cent of the total pleural surface. One hundred and one persons with apical scars had adhesions covering an average area of 9 per cent of the pleura. Sixty-nine persons with calcified nodules had an average pleural area of 8 per cent involved. Fifty-two persons with no nodules, scars or other chronic lesions had an average area of 10 per cent of the pleura involved. The average surface area of pleura covered by adhesions in the pneumonia-pleurisy group was at least twice the average surface area covered in any and all other groups.

TYPE AND LOCATION OF ADHESIONS

The fibrous pleural adhesions in the 400 unselected autopsy subjects were classified as (1) diffusely arranged or (2) isolated strands. Four general locations were arbitrarily chosen as (1) anterior, (2) posterior, (3) upper and (4) lower parts of the pleura (table 2). Many pleurae showed both diffuse and isolated types of adhesions, and a majority of the specimens showed adhesions in more than one location.

In the group with past histories of pneumonia or pleurisy or both there were isolated adhesions in 57 per cent and diffuse adhesions in 59 per cent. It was striking that in the remaining groups the incidence of diffuse adhesions was low. This suggested that the adhesions in the pneumonia group tended to be diffuse and that the incidence of isolated adhesions in this group was relatively low because the diffuse adhesions obscured the isolated ones.

From the data in table 2 it is evident that most of the pleural adhesions were located over the posterior aspect of the lungs. In the pneumonia group the extensiveness of the diffuse adhesions served to increase the incidence in all locations. However, the predominance of adhesions in the posterior location was maintained throughout. The anterior location was a less frequent site. The lower parts of the pleura were the sites of fibrous adhesions much more frequently than the upper

TABLE 2.—*Types and Locations of Fibrous Pleural Adhesions* *

	Group with Pneumonia, %	Group with Apical Scars, %	Group with Calcified Pulmonary Nodules, %	Group with No Tuberculosis or Pneumonia, %
Type of adhesion:				
Isolated	57	76	81	73
Diffuse	59	27	29	35
Location:				
Posterior	85	65	69	67
Anterior	69	42	50	65
Lower	49	35	23	38
Upper	26	28	20	12

* The most common fibrous pleural adhesion is an isolated one occurring over a lower lobe posteriorly.

parts, which include the apexes. From these findings it is evident that the most common fibrous pleural adhesion in this series was an isolated one occurring posteriorly over a lower lobe.

MICROSCOPIC TYPES

The great majority of the adhesions observed were delicate fibrous structures which were additions to the pleura and were not associated with permanent changes in the parenchyma beneath. There was slight subpleural thickening beneath and around the typical fibrous pleural adhesion. The thickening was composed of fibrous tissue between the pleura and the definite subpleural elastic layer. The thickening was most prominent beneath the point of adhesion and gradually became thinner away from the point. As a rule, isolated and diffuse adhesions did not differ except in extent.

A few of the adhesions disrupted the subpleural elastic layer and were composed of abundantly vascularized fibrous tissue. Lesions of this type did not constitute a significant percentage of the adhesions in the specimens observed.

COMMENT

That fibrous pleural adhesions are associated with inflammations of the lungs is supported by the statistical evidence presented in the foregoing paragraphs. Pneumonia is the most common and outstanding related disease. Persons who have had pneumonia or pleurisy or both have a high incidence of adhesions that are extensive. Further, the locations of the adhesions in persons who have had pneumonia correspond to the more common sites of pneumonia; i. e., they are to be found posteriorly on the lower lobes. Fibrous adhesions are not congenital. Newly born infants do not have them, and the incidence increases as time permits the development of associated conditions. Lungs with focal inflammation frequently present evidence that inflammation is related to adhesions. This is most convincing in a young person showing isolated fibrous strands over an area involved by a solitary abscess, over a lingula of the lung showing bronchiectasis or only in the vicinity of a tuberculous cavity. Infarcts of the lung may have associated overlying adhesions.[1] The inflammation of the pleura over the infarct probably is the principal causal factor.

Most fibrous pleural adhesions are without historical or anatomic evidence to suggest a related disease or condition. Perhaps the cause is not manifest clinically; the patient may forget the incident; the doctor may obtain an incomplete past history; the methods of examination may be inadequate, or the predisposing condition may leave no permanent change except the adhesions.

Masses and nodules of a cancer are related to fibrous pleural adhesions only when inflammation occurs with them. Carcinoma of the bronchus frequently causes obstruction of the bronchial lumen with subsequent atelectasis and pneumonia. Adhesions form over the inflamed portion of the lung and not in the vicinity of the obstructing mass of tumor. Metastatic nodules of tumor from remote organs do not commonly predispose to pneumonia and therefore are not associated with adhesions. Strands of tumor tissue in subpleural lymphatic channels do not produce an appreciable inflammatory reaction.

Although tuberculosis is an inflammatory disease, there is scant evidence that subclinical and latent lesions are associated with fibrous pleural adhesions. The adhesions over the lungs of the group with calcified nodules, with or without scars of the apexes, are not significantly different in incidence, extent, location and type from those in a similar age group without such lesions. Only occasionally an isolated fibrous adhesion is located over a calcified nodule. Of the apical scars having overlying fibrous adhesions there are some which are convincing in their relation. Microscopically, these few adhesions are dense fibrous

1. Castleman, B.: Arch. Path. **30**:130, 1940.

strands that are continuous with the fibrous tissue of the apical scars. Blood vessels with muscular walls are continuous from the scars through the adhesions to the parietal pleura. The subpleural elastic and fibrous layers are interrupted, although the scar contains persistent elastic tissue which preserves the outlines of the obliterated alveoli.

From the observations on a few lungs showing radiation pneumonitis there is no evidence that fibrous pleural adhesions are directly a result of roentgen ray irradiation. Warren and Gates,[2] from experimental and pathologic observations, stated that "extensive fibrosis and pleural adhesions may be ascribed to inflammation or infection, intercurrent or resulting from the radiation-induced changes." Their view is in accord with the idea that inflammation is the basic cause of fibrous pleural adhesions.

Patients giving either historical or anatomic evidence of rheumatic fever show no increase in the incidence of fibrous pleural adhesions. Likewise, patients with advanced mitral stenosis and fibrous pericardial adhesions do not show an increase in incidence of adhesions of the pleura. However, a few specimens from persons with active rheumatic heart disease showed adhesions of the pleura limited to the region of the pericardium. From these observations it appears that in an occasional case active rheumatic heart disease is accompanied by fibrous pleural adhesions near the heart.

Arteriosclerosis and arteriolosclerosis of the pulmonary arteries, observed grossly and microscopically, do not show a relation to adhesions of the pleura. It is true that blood vessels show sclerosis when they course in scars of the apexes, around chronically inflamed lesions of bronchiectasis, near abscesses and about tuberculous cavities. However, this alteration may be considered a result of the inflammation. The only suggestion of an association is that single isolated adhesions are attached over interlobular septums in numerous instances, and the only accompanying lesion is sclerosis of the vessels in the septum.

One group of 35 specimens was from persons killed accidentally and without preceding manifest disease. A comparison of this group with the specimens from persons with chronic diseases showed no significant difference in the incidence of fibrous pleural adhesions.

The specimens from patients with manifest diseases were divided into groups including (1) those with chronic cardiac disease, (2) those with cancer, (3) those with chronic infections and (4) those with acute infections. The curve of incidence of fibrous pleural adhesions in these groups corresponded to the curve of the average age of the persons in the groups. Otherwise there were no significant differences in incidence or in location of the adhesions.

2. Warren, S., and Gates, O.: Arch. Path. **30**:440, 1940.

Besides the several conditions already discussed, other possible factors were studied. The following could not be shown to be of significance: race, sex, increased blood pressure, inhalation anesthesia, emphysema of the lungs, anthracosis of the lungs, duration of primary disease, cause of death and economic status of the subject.

SUMMARY

Sixty-six per cent of the pairs of lungs obtained at 400 unselected autopsies showed fibrous pleural adhesions. The incidence of fibrous pleural adhesions increased with age. Of 49 patients giving a past history of pneumonia or pleurisy or both, 94 per cent had fibrous pleural adhesions, which were twice as extensive as the adhesions in groups without a history of pneumonia. The most common pleural adhesions were isolated ones occurring over the lower lobes posteriorly. One sixth of the apical scars were associated with fibrous pleural adhesions. Two thirds of the apical adhesions were not over scarred apexes. The great majority of fibrous pleural adhesions were over essentially normal pulmonary tissue.

FORSSMAN'S "CAROTID SYNDROME"

A CONTRIBUTION TO THE STUDY OF ANAPHYLACTIC CHANGES IN THE NERVOUS SYSTEM FROM THE STANDPOINT OF PATHOLOGY

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The term "carotid syndrome" is used by Forssman [1] to denote neurologic disturbances occurring in the guinea pig when a small dose of serum containing Forssman antibodies is injected into the carotid artery. This syndrome consists of disequilibrium, rotary movements along the vertical and the longitudinal axis, forced deviation of the eyeballs and nystagmus. Manifestations of anaphylactic shock which are commonly observed when Forssman serum is injected intravenously are absent or scanty. Under these experimental conditions the serum, which is slowly injected centripetally into the right carotid artery, reaches through the subclavian and vertebral arteries, the hindbrain and the midbrain, where a reaction presumably takes place between Forssman antibodies in the injected serum and Forssman antigen normally present in the nervous tissue. That Forssman antibodies are responsible for the syndrome is apparent from the fact that no clinical manifestations occur when these antibodies are removed from the serum either by absorption with guinea pig kidney or by heating at 80 C. However, a similar syndrome is produced by injecting large amounts of normal rabbit, ox or eel serum, cobra venom (Friedberger and Oshikawa [2]) and suspensions of lycopodium or starch (Forssman [1c]).

Although the serologic problems concerning this syndrome have been the object of numerous investigations, little has been published on its pathologic aspects. Friedberger and Schröder [3] reported the pathologic changes occurring within forty-eight hours in 8 guinea pigs as studied in the Nissl and hematoxylin-eosin preparations. Lesions of necrotic nature were found which were considered vascular in origin; there were

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From the Research Department of Letchworth Village.

1. Forssman, J.: (*a*) Biochem. Ztschr. **110**:164, 1920; (*b*) **133**:114, 1922; (*c*) Acta path. et microbiol. Scandinav. **3**:749, 1926.

2. Friedberger, E., and Oshikawa, K.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **33**:48, 1922.

3. Friedberger, E., and Schröder, P.: Ztschr. f. d. ges. exper. Med. **26**: 287, 1922.

no hemorrhages, no thromboses and no softenings. Ingvar [4] and Skoog [5] briefly reported the observation of capillary hemorrhages in the medulla oblongata in guinea pigs which had died a few hours after the injection. Finally, Skoog [6] and Broman,[7] using the method of vital staining, found increased permeability of the hematoencephalic barrier in the regions which are reached by the Forssman serum.

In view of this scarcity of pathologic reports, it was considered of interest to study the lesions underlying the "carotid syndrome." It was thought, moreover, that such investigation might offer additional data for the solution of the previously investigated problem of the pathologic aspects of anaphylactic reactions in the central nervous system (Jervis and co-workers [8]).

METHODS

Two types of Forssman serum were used. The first was obtained from rabbits given six injections of an aqueous extract of guinea pig kidney over a period of three weeks. The extract was freshly prepared by grinding two kidneys in a mortar with approximately 20 cc. of saline solution; the suspension was centrifuged at low speed, and the supernatant fluid was injected intravenously into the marginal vein of the rabbit's ear. The second type of serum was obtained from rabbits prepared by injecting 10 to 15 cc. of a 5 per cent suspension of fresh sheep red cells twice a week over a period of three weeks. The rabbit serum, obtained one week after the last injection, was inactivated at 60 C. for thirty minutes. Both serums produced typical "reversed" anaphylactic shock when injected intravenously into guinea pigs at doses of 1 to 2 cc.

Doses of 0.1 to 0.3 cc. diluted to 0.5 cc. with physiologic solution of sodium chloride were injected slowly (over eight to ten seconds) into the right carotid artery in guinea pigs in the centripetal direction. The artery was tied distally from the site of injection shortly before the injection and proximally to the site of injection immediately after. Some 50 guinea pigs were given these injections. The animals were killed and autopsies made at various intervals from a few minutes to several days. The central nervous system was fixed either in solution of formaldehyde or in alcohol, and the following stains were used: Nissl's for neuron cells, Spielmeyer and Weil stains for myelin sheaths, Bodian's for axis cylinders, Pickworth's for blood vessels, Wilder and Mallory's for connective tissue, Holzer's, Cajal's and Hortega's for glia and scarlet red for fatty products of degeneration. In a few cases, intravital staining of the central nervous system was obtained by injecting intravenously 10 to 15 cc. of a 1 per cent solution of trypan blue a few minutes after the administration of serum.

In addition, 5 guinea pigs were given 0.3 cc. of Forssman serum subdurally through a trephine opening in the skull. Finally, 10 animals were given intracarotid injections of a 5 per cent suspension of starch.

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4. Ingvar, S.: Acta path. et microbiol. Scandinav. **4**:349, 1927.
5. Skoog, T.: Acta oto-laryng., 1939, supp. 32, p. 1.
6. Skoog, T.: Acta oto-laryng. **25**:365, 1937.
7. Broman, T.: Skandinav. Arch. f. Physiol. **80**:59, 1938.
8. Jervis, G. A.; Ferraro, A.; Kopeloff, L., and Kopeloff, N.: Arch. Neurol. & Psychiat. **45**:733, 1941.

RESULTS

In the majority of animals which were given the intracarotid injection of Forssman serum the typical "carotid syndrome" occurred. Its clinical manifestations corresponded closely to those described by Forssman [1] and Skoog.[6] Immediately after the injection there was observed forced rotation of the head and spine to the left; the limbs on the right side were in spastic extension and exhibited tremors and clonic movements. When the animal was left free, it showed a tendency to move in a circle counterclockwise. In addition, there was rotation along the longitudinal axis to the left (sinistrotorsion). The eyes showed deviation, the right eye toward the nose and the left one in the opposite direction. Nystagmus was frequently observed. This syndrome lasted from a few minutes to several days. About 50 per cent of the animals died. The other animals at times recovered completely and at other times showed various neurologic disturbances, such as tremors, paralysis of limbs and tilted position of the head.

The "carotid syndrome" was occasionally observed also in the animals which were given suspensions of starch. It was much less constant and less characteristic. No animals of this group died, and in no instance did the symptoms last more than one hour.

Following the subdural injection of Forssman serum, the guinea pigs showed jerking movements, repeated convulsions and coma; all these animals died within twenty-four hours.

For a description of the pathologic observations, the animals showing the typical "carotid syndrome" may be divided into three groups according to the periods of time elapsing between the injection of Forssman serum and death.

The first group includes the animals which died or were killed within twelve hours after the injection. It consisted of 18 guinea pigs, 10 of which were fixed in solution of formaldehyde and 8 in alcohol. The pathologic picture in the Pickworth preparation was characteristic (fig. 1). The blood vessels of the right half of the medulla oblongata were dilated. A striking difference of vascular pattern between the two halves of the medulla thus resulted. Several degrees of vasodilatation were seen, which were usually correlated with the intensity of the clinical symptoms. When marked dilatation had taken place, small hemorrhages were observed (fig. 1 *C*). These, however, were seen only in animals which showed severe symptoms followed shortly by death. The vasodilatation often extended to the right half of the pons and, to a lesser extent, to the cerebral pedunculus. The right half of the cerebellum occasionally showed vascular dilatation. No hemorrhages were seen in these regions. The endothelium of the dilated vessels often showed swelling in the hematoxylin-eosin preparations. Edema of the perivascular space was frequently seen, but perivascular infiltration was absent. The nerve cells as seen with the Nissl method showed diffuse alterations in the areas of vascular dilatation. Swelling of the cell and chromatolysis were the most frequently encountered lesions, while vacuolation of the cytoplasm was rarely seen. These lesions were more pronounced in

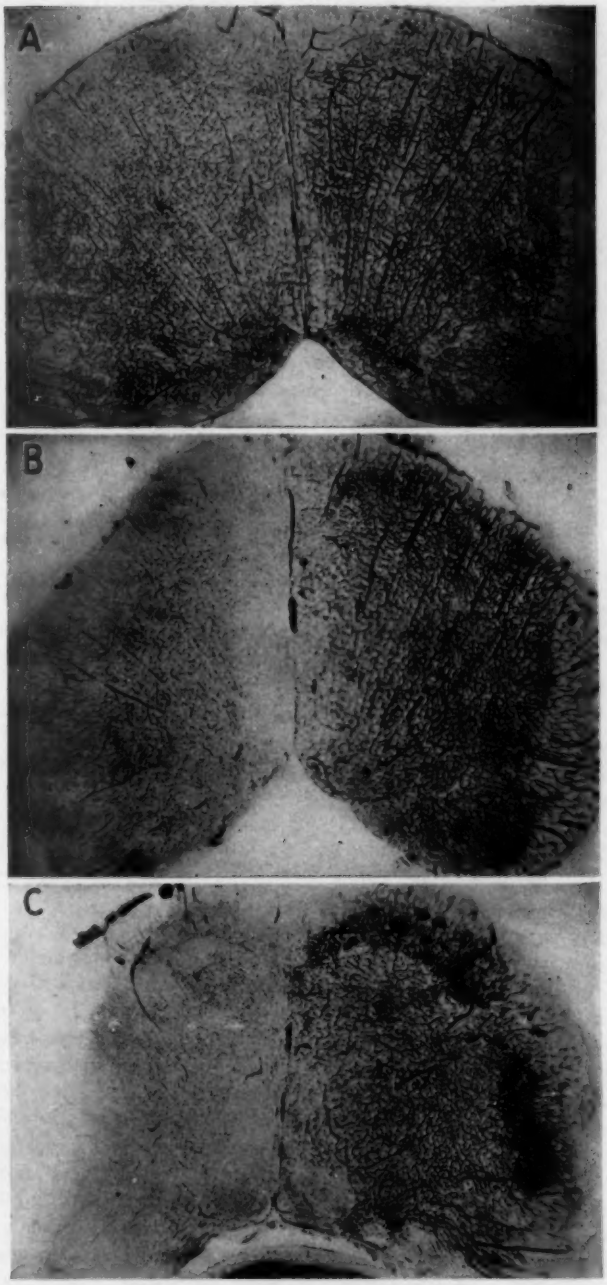

Fig. 1.—Various degrees of vascular dilatation in the right half of the medulla oblongata. Pickworth stain; low power magnification.

the animal that died several hours after the injections. The glia showed no apparent reaction. In the myelin preparation the right half of the medulla was frequently paler than the left half. This appeared to be due to edema which infiltrated among the myelin sheaths more than to actual destruction. However, occasionally some swelling and breaking down of individual sheaths could be observed in the affected areas.

A second group includes the animals which died or were killed between twelve and forty-eight hours after the injection of Forssman serum. It included 9 animals, 4 of which were fixed in solution of formaldehyde and 5 in alcohol. The Pickworth preparation showed vascular dilatation as described in the previous group only in a few instances, those in which death occurred before the eighteenth hour. Later on, the vascular pattern appeared normal with the exception of occasional small hemorrhages. In a few cases in which considerable edema was present in the affected half, the blood vessels appeared smaller than those in the normal side. Diffuse alterations of the nerve cells, more pronounced than in the previous group, were observed. They consisted of swelling of the cell body with chromatolysis and disappearance of the nucleus (fig. 2*A*) or vacuolation and shrinkage of the cytoplasm with nuclear pyknosis (fig. 2*B*). A characteristic lesion appeared in animals of this group from twenty-four to forty-eight hours after the injection. It consisted of small scattered foci of "softening." In the hematoxylin-eosin and the Nissl preparations these foci appeared as small areas of bleaching; the nerve cells had disappeared or were severely degenerated, and only fragmented nuclei and cellular detritus were seen. The glia cells appeared likewise damaged, showing no reactive elements at this stage. In the myelin preparation the foci appeared as demyelinated patches; fragments of myelin sheaths and swollen fibers were seen particularly at the periphery. In the silver preparation the axis-cylinders were partly destroyed. No fatty material was detectable with scarlet red. The foci contained no hemorrhages or hematogenous elements, such as lymphocytes or leukocytes. There was apparently no constant relation to blood vessels; although blood vessels were present within the focus, the lesion was rarely perivascular. These foci were scattered irregularly in the right half of the medulla and pons. Occasional foci were seen in the cerebellar pedunculi and midbrain. They varied in size from very small to large ones, the latter occupying about one eighth of the medulla. The configuration was generally irregular, roundish shapes predominating over elongated ones.

A third group includes 8 guinea pigs which had lived from five to ten days after the injection. In the Pickworth preparation no significant alterations were found. In the Nissl preparations, lesions of the nerve cells such as those seen in other groups were scanty. The characteristic feature of this group consisted of the presence of scattered foci that in distribution, size and shape were similar to the foci described in the previous group. In the myelin preparation (fig. 3) the foci appeared as sharply defined areas of demyelination; the destruction of myelin was complete, and only in a limited peripheral zone were swellings and fragmentations of myelin sheaths discernible. In the silver preparation a considerable number of the axis-cylinders within the lesions were destroyed; the remaining ones showed irregular swellings and fragmentations. With cellular stains (fig. 4) the lesion was seen to be filled with compound granular elements. These in the Nissl and hematoxylin-eosin stains showed large amounts of foamy cytoplasm and small eccentric nuclei; with the Herxheimer stain, the cytoplasm contained characteristic red granules of fat. Occasionally, large compound granular cells containing two nuclei were present, but giant cells were not seen. Hematogenous elements, such as lymphocytes, plasma cells and leukocytes, were scanty.

Macroglia cells were absent within the patch; only at the periphery and in the adjacent normal nervous parenchyma some evidence of macroglial reaction could be observed; hypertrophic and hyperplastic macroglial elements were present

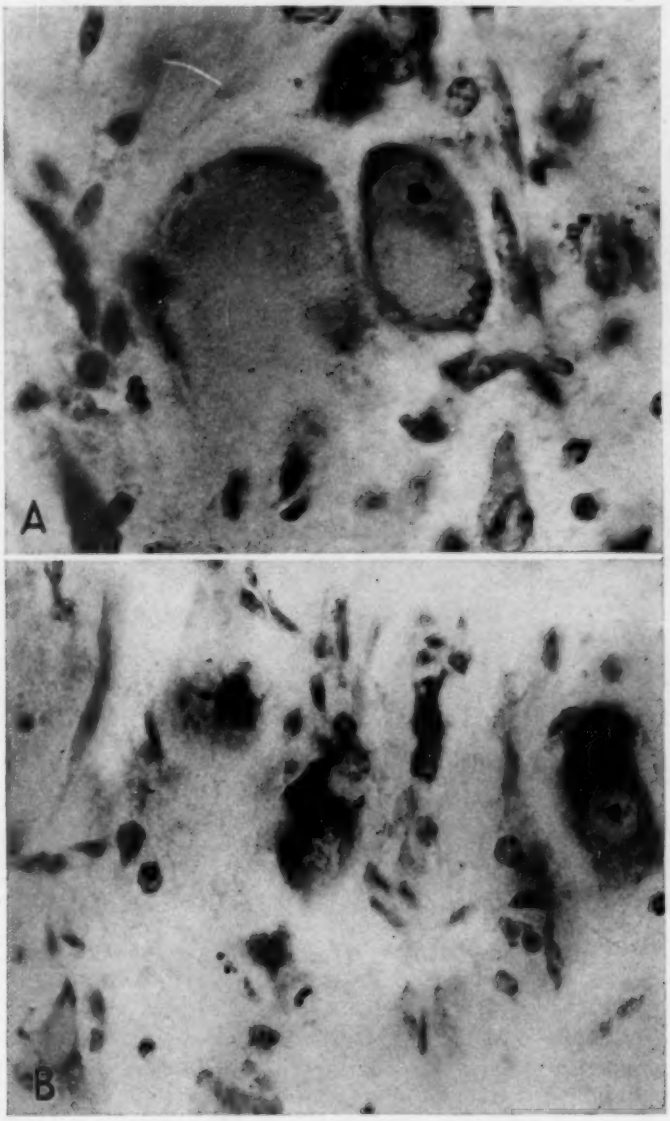

Fig. 2.—Degenerative changes of the nerve calls: *A*, swelling and chromatolysis. *B*, vacuolation, shrinkage and shadow cell. Nissl stain; high power magnification.

here. Occasionally, degenerative types of glia cells were seen. In the Hortega preparation the periphery of the lesion disclosed various phases of transformation

of microglia cells into compound granular elements. The connective tissue stain revealed no connective fibers within the lesion. In the Mallory preparation the blood vessels showed no evidence of thrombosis. There were no hemorrhages. The vessel walls were often thickened owing to proliferation of the intima and adventitia.

In the animals in which vital staining was done, the pathologic picture was very characteristic: The right half of the medulla, pons and cere-

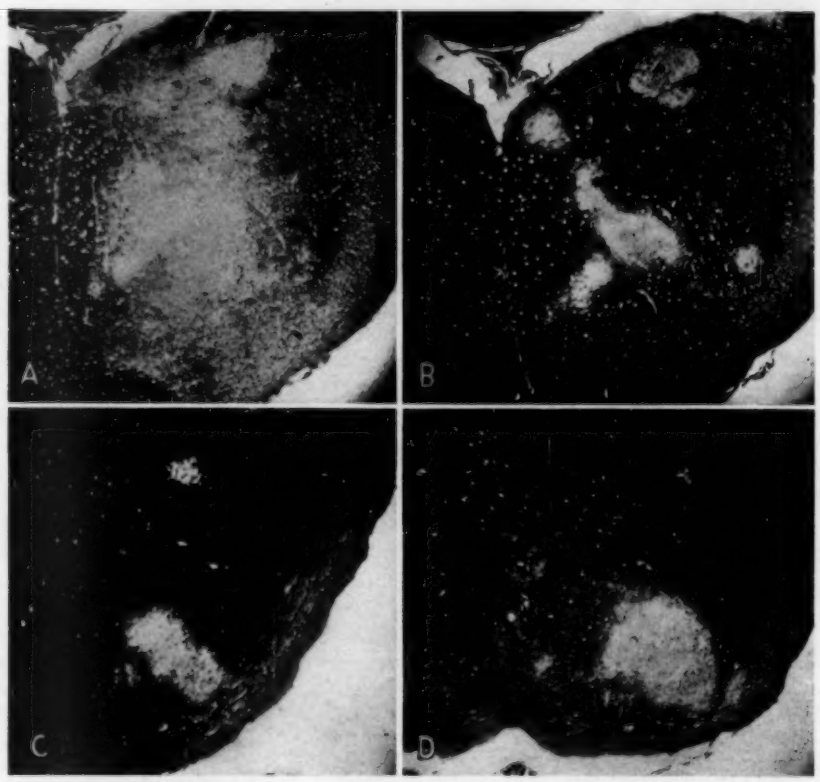

Fig. 3.—Circumscribed foci of demyelination in the medulla oblongata (*A* and *B*), in the cerebral pedunculus (*C*) and in the pons (*D*). Weil stain; low power magnification.

bellum showed an intense blue color, while the other parts of the central nervous system remained unstained.

The animals which had received starch suspension into the carotid artery and which exhibited neurologic disturbances showed mainly vascular changes. In the Pickworth preparations of the medulla the vascular pattern of the right half was altered, showing localized areas of anemia and hyperemia with frequent small hemorrhages. There were

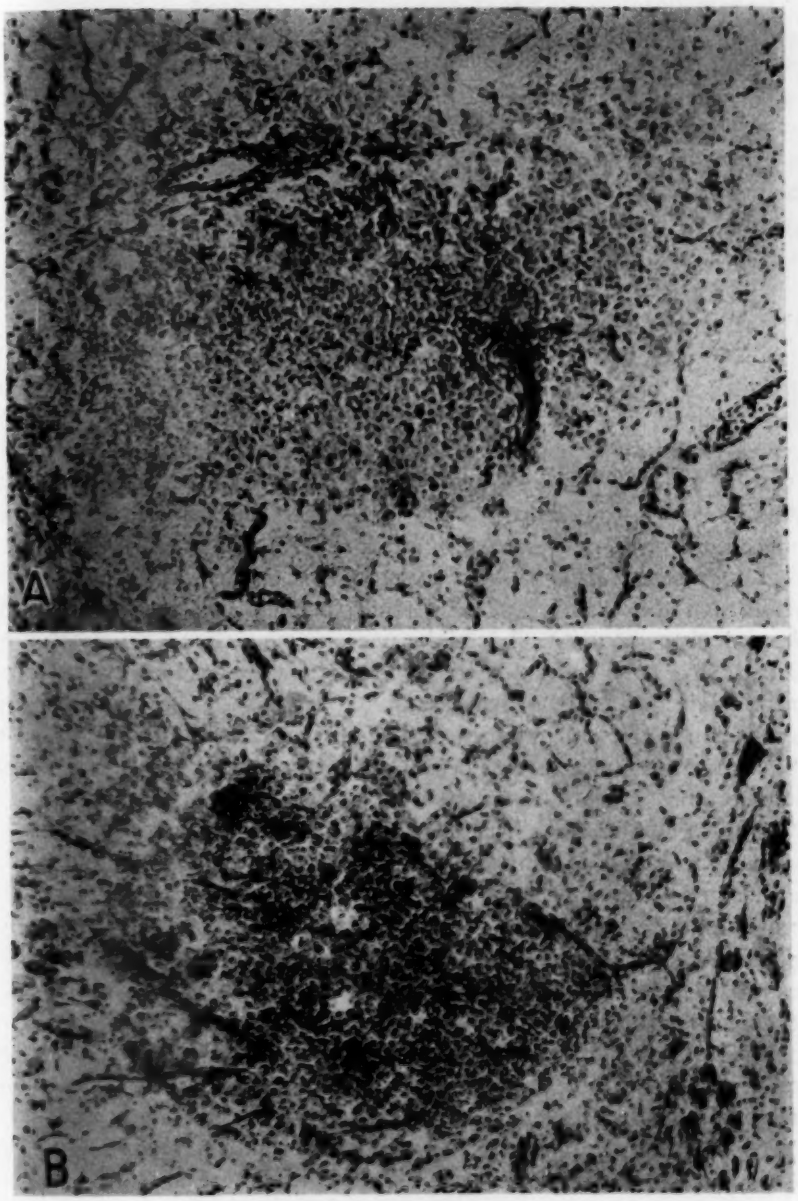

Fig. 4.—Foci of demyelination in the Nissl preparation showing mainly compound granular corpuscles. Nissl stain; medium power magnification.

no diffuse changes in the neuron cells, no circumscribed foci of demyelination and no microglial reaction.

The pathologic changes in the animals which received the subdural injection of Forssman serum consisted of pronounced congestion of the meningeal blood vessels and infiltrations of the pia with leukocytes and lymphocytes. Subpial hemorrhages were frequently seen; in 1 instance there were small perivascular hemorrhages in the external cortical layer and in the periventricular regions.

COMMENT

The histologic picture of the "carotid syndrome" brought about by Forssman serum is vascular and parenchymatous in character. In the first stage, the blood vessels in the areas reached by the Forssman serum are dilated and congested, endothelial damage is apparent and small hemorrhages may occasionally occur. That the damage to the blood vessels brings about an abnormally increased permeability of the hematoencephalic barrier appears from the results of experiments with vital staining. It is well known that when trypan blue or similar dyes are injected intravenously into a normal animal, no part of the central nervous system retains the dye, a hypothetic barrier between the blood vessel and the brain preventing the coloring substance from passing through the vascular wall into the nervous parenchyma. However, as Skoog [6] and Broman [7] reported, when a dye is given following an intracarotid injection of Forssman serum, one half of the medulla, pons and cerebellum is markedly stained, thus indicating that a breaking down of the hematoencephalic barrier occurs in the region reached by the Forssman serum.

This "vascular stage" is followed in a certain number of cases by parenchymatous lesions, both diffuse and patchy in distribution, the former being characterized by degenerative changes of the neuron cells and a mild reaction of the glia, the latter by circumscribed foci of softening. The histologic characteristics of the circumscribed foci correspond closely to those described by Hassin [9] in "multiple degenerative softenings." In this condition the softened areas are in the form of multiple irregularly scattered patches of demyelination which do not follow the tracts of nerve fibers and do not depend on territorial blood supply. The blood vessels show neither thrombosis nor embolism. Compound granular corpuscles of microglial origin constitute the content of the softened foci. Fibers of connective tissue are absent, and there is no formation of a scar or a capsule.

The parenchymatous lesions may be explained by assuming that the Forssman antibodies, passing through the impaired hematoencephalic barrier, come in contact with antigen normally present in the tissue of

9. Hassin, G. B.: J. Neuropath. & Exper. Neurol. **1**:200, 1942.

the guinea pig. A reaction between antigen and antibody takes place, resulting in damage of the nervous parenchyma. This reaction may be considered of anaphylactic nature, following the widely accepted definition of Doerr [10] that the common character of anaphylactic phenomena is the reaction between antigen and antibody at the cellular site of the antibody or the antigen. Commonly the antibody is present in the cells and the antigen is of exogenous origin, while in the present experiments the antigen is present in the tissue and the antibody is injected. That the reaction of Forssman's antigen and antibody represents a local anaphylactic phenomenon appears to be substantiated by the results of the subdural administration of Forssman's antibodies in guinea pigs. A severe rapid reaction was obtained, characterized by necrosis of the walls of blood vessels, edema and degeneration of connective fibers of the meninges, hemorrhages and infiltration with leukocytes. As is well known, these morphologic features are characteristic of the Arthus phenomenon. Kallos and Kallos-Deffner [11] recently described similar changes in the peritoneum of the guinea pig following the injection of Forssman serum and concluded that these findings represent manifestations of local anaphylaxis.

It appears possible that local anaphylactic reactions occur also in the endothelial cells of the blood vessels, before the antibodies reach the parenchyma. Evidence in favor of this hypothesis explaining the vascular damage referred to in the foregoing section on an anaphylactic basis is offered by the observations of Kallos and Kallos-Deffner [11] and Halber [12] indicating that large amounts of Forssman antigen are present in the vascular endothelium of the "cavia group" of animals.

On the basis of these results the symptoms comprised in the carotid syndrome are easily explained: Unilateral parenchymatous lesions of the vestibular nuclei will result, in fact, in disequilibrium, forced rotary movements and nystagmus. The same symptoms are likely to occur also when vascular changes and reversible cellular alterations take place as in the animals that recovered spontaneously and showed little, if any, parenchymatous alterations. The occurrence of a transitory and often incomplete carotid syndrome following the injection of starch apparently also indicates a vascular mechanism; in this case, however, the damage of the blood vessels and the consequent impairment of the cellular function are brought about by small embolisms independently of any anaphylactic phenomenon.

Of particular interest appear to be the circumscribed lesions of demyelination and microglial reaction found in the animal that showed marked symptoms for a period of more than a week. Similar lesions

10. Doerr, R.: Ztschr. f. Hyg. u. Infektionskr. **118**:623, 1936.

11. Kallos, P., and Kallos-Deffner, L.: Schweiz. Ztschr. f. allg. Path. u. Bakt. **5**:97, 1942.

12. Halber, W.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **39**:282, 1924.

have been previously found to occur in the central nervous system of the monkey given extract and emulsion of rabbit brain (Rivers and Schwentker [13]; Ferraro and Jervis [14]); it was then assumed that the pathologic changes were due to brain-specific antibodies, the reacting antigen being a lipoid present in the extract activated by a heterologous protein contained in the emulsion. Moreover, scattered demyelinating lesions of the same type were found in the brains of monkeys in which anaphylactic shocks had been produced in various ways (Jervis and co-workers [8]); the hypothesis was advanced that an antigen-antibody reaction was at the basis of the demyelinating lesion, the brain-specific antibodies being the product of complete antigens formed by the injected foreign protein acting on the damaged brain tissue. The circumscribed lesions of demyelination here described, which apparently are also the result of an antigen-antibody reaction within the central nervous system, show similar histologic characteristics, although hematogenous elements were rarer and giant cells absent. Differences in the properties of the antigen and the antibody and the intensity of the reaction may explain these differences in histologic details.

Evidence has been thus accumulating which indicates that scattered demyelinating lesions of the central nervous system ("multiple degenerative softenings") can be experimentally produced at the site of an antigen-antibody reaction. Such findings may eventually offer some clue in the study of the genesis of certain demyelinating conditions in man, the nature of which is still unknown.

SUMMARY

The pathologic changes which underlie Forssman's "carotid syndrome" in the guinea pig are described. This syndrome occurs when Forssman antibodies are injected into the right carotid artery. The right half of the hindbrain and midbrain was found to show marked dilatation of blood vessels and damage of the endothelium, followed by parenchymatous lesions. These consisted of diffuse degenerative changes of nerve cells and circumscribed foci of demyelination with microglial reaction ("multiple degenerative softenings"). The parenchymatous lesions are considered to be anaphylactic in nature, resulting from the reaction of Forssman antibodies which have passed through an impaired hematoencephalic barrier with Forssman antigens normally present in the tissue of the guinea pig.

From these and similar findings previously reported, it is apparent that scattered demyelinating lesions of the central nervous system ("multiple degenerative softenings") can be experimentally produced at the site of an antigen-antibody reaction.

13. Rivers, T. M., and Schwentker, F. F.: J. Exper. Med. **61**:689, 1935.
14. Ferraro, A., and Jervis, G. A.: Arch. Neurol. & Psychiat. **43**:195, 1940.

NEUROBLASTOMA OF THE MEDIASTINUM WITH PHEOCHROMOBLASTOMATOUS ELEMENTS

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Tumors arising from the sympathetic nervous system have been the object of much interest and study. The first case adequately described was that reported by Virchow in 1864 (Wahl [1]; Lewis and Geschickter [2]), a case of ganglioneuroma of the mediastinum. Exhaustive reviews of the literature have been made by Dunn,[3] Blacklock,[4] Reid,[5] McFarland,[6] Lewis and Geschickter,[2] Raska and Skorpil (Fingerland [7]) and Wahl.[1] The majority of these new growths spring from the adrenal medulla, but they have been reported as arising from many parts of the body.

The three general types of sympathetic nerve tumors—ganglioneuroma, neuroblastoma and paraganglioma (pheochromocytoma)—represent cell types of different degrees or phases of differentiation from the primordial sympathetic cells, the sympathogonia. Arrested cells in any stage of development may give rise to neoplastic growth anywhere in the sympathetic system, producing a tumor of that cell type or of a mixture with numerous stages of differentiation present. Further, as has been predicted by Lehman,[8] Blacklock,[4] Lewis and Geschickter [2] and Wahl,[1] a mixture of undifferentiated cells, well developed ganglion cells, pheochromoblasts and pheochromocytes, and glial cells should be found in some cases.

Wahl and Craig [9] reported a case with three distinct tumors all in different stages of development, neuroblastoma, ganglioneuroma and

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1. Wahl, H. R.: J. M. Research **30**:205, 1914.
2. Lewis, D., and Geschickter, C.: Arch. Surg. **28**:16, 1934.
3. Dunn, J. S.: J. Path. & Bact. **19**:456, 1915.
4. Blacklock, J. W. S.: J. Path. & Bact. **39**:27, 1934.
5. Reid, M.: Ann. Surg. **88**:516, 1928.
6. McFarland, J.: Arch. Path. **11**:118, 1931.
7. Fingerland, A.: J. Path. & Bact. **67**:631, 1938.
8. Lehman, E. P.: J. M. Research **31**:309, 1917.
9. Wahl, H. R., and Craig, P. E.: Am. J. Path. **14**:797, 1938.

ganglioneuroblastoma. Cushing and Wolbach [10] removed a portion of a tumor in the back of an infant and found it to be sympathicoblastoma. Laminectomy done at the same site ten years later, the child having received only a mixture of erysipelas and prodigiosus cultures (Coley's toxin) in the interim, revealed an intraspinal extradural ganglioneuroma, which was removed. A transformation had taken place by further differentiation from sympathoblasts to ganglion cells. Although various mixtures have been found, the paragangliomatous (pheochromoblastomatous) elements tend to be more in the pure state. Lewis and Geschickter,[2] however, reported 2 cases of malignant paraganglioma in which neuroblasts were present.

In 5 of the 51 cases of ganglioneuroma reviewed by Dunn [3] in 1915, the thorax was the site. The first case of thoracic ganglioneuroma was reported by Loretz in 1870. Bigler and Hoyne [11] reported a case in 1934 and reviewed the previous 11 cases reported out of a total of 164 cases of ganglioneuroma. Raska and Skorpil (Fingerland [7]) in 1936 found 25 cases of ganglioneuroma of thoracic origin. Two proved cases have been reported since that time, bringing the total to 27. Neuroblastoma of the mediastinum is less frequent, but 13 cases have been reported out of approximately 200 cases of neuroblastoma in the entire literature. Although paraganglioma in general, including the carcinoid tumors, is the most frequent of the three types (Reid [5]), adult chromaffin tumors are rare, according to Philips,[12] who reported one of thoracic origin and made the most recent survey of the literature, to October 1940, finding only 82 cases, in 11 of which the tumor occurred outside the adrenal glands; in 9 of these it was found in Zuckerkandl's organ, which lies at the aortic bifurcation, and in only 1, in the mediastinum.

REPORT OF A CASE

A white boy aged 4 years was first admitted to the Children's Pavilion of the University of Kansas Hospitals (service of Dr. F. C. Neff), March 25, 1940, with swelling in the right side of the neck, noted first in December 1939. Fever, anorexia, loss of weight, occasional pain in the knees and elbow and slight cough with expectoration had been present for about six weeks. The patient was a thin, poorly nourished boy with a few enlarged, firm, knotty, slightly tender lymph nodes in the right supraclavicular fossa, exaggerated breath sounds anteriorly and an edge of the liver 2 cm. below the costal margin. There was slight secondary anemia; the red blood cell count was 3,870,000, the hemoglobin content 10.8 Gm. (70 per cent) and the white cell count 9,900 with 51 per cent polymorphonuclears. A roentgenogram of the chest revealed a mass 2 cm. in diameter in the right peritracheal area at the level of the first rib anteriorly with a larger

10. Cushing, H., and Wolbach, S. B.: Am. J. Path. **3**:203, 1927.

11. Bigler, J. A., and Hoyne, A.: Am. J. Dis. Child. **43**:1552, 1932.

12. Philips, B.: Am. J. Path. **30**:916, 1940.

surrounding shadow in the whole upper lung field. Biopsy of the cervical nodes was reported as showing "neuroblastoma, metastatic in lymph nodes."

On the second admission, March 30, the patient received a course of treatment with high voltage roentgen rays, directed to the right upper side of the chest and the lumbar portion of the spinal column and was discharged in four weeks showing little change, though somewhat weaker. However, the thoracic mass was considerably reduced in size.

Three months later the child began to complain of pains in the fingers, legs and toes and of soreness of the scalp. He was much weaker; large firm fixed nodules were palpable over the skull, multiple shotty nodes were present in the neck and the right supraclavicular mass was considerably enlarged. The anemia had progressed. Roentgenograms revealed extensive metastases in the skull, the ribs, the pelvis and nearly all of the long bones, with a peculiar periosteal elevation. The patient was given high voltage roentgen radiation, and anodynes were administered to control pain. Death occurred five weeks later.

Autopsy.—The essential findings were in the thorax. The heart was flabby and moderately dilated. The pleural cavities contained straw-colored fluid, 300 cc. on the right and 100 cc. on the left. The left lung presented no abnormality except three small round nodules, 2 mm. in diameter, in the lingula of the lower lobe; these were grayish white on section and quite firm in consistency. On the right side, occupying the upper third of the thoracic cavity, a large tumor mass, 6 cm. in diameter, compressed the upper lobe of the right lung downward and forward so that only a compact rim of this lobe remained. The middle lobe was bluish gray and definitely atelectatic, but the lower lobe showed nothing unusual. The large tumor mass was sharply demarcated from the lung, showing partial encapsulation, but it was tightly adherent to the upper three ribs on the right posteriorly and to the large firm nodular mass of lymph nodes in the supraclavicular fossa. It pressed against the upper three thoracic vertebrae medially but had not directly invaded them. The trachea was pushed slightly to the left and the innominate vein and artery were compressed and drawn out over the surface of the tumor mass. The mass itself was egg shaped, fairly smooth in contour except where invasion had taken place in the neck, pale pink and moderately firm in consistency. Sections through the middle of the tumor presented an uneven, cellular-appearing pale pink surface, while sections from the lower portion showed a patchy pale red and yellow color and an irregular patchy friable consistency alternating with soft tissue and other areas of firm dense white tissue.

The liver was enlarged, weighing 680 Gm., and multiple small grayish nodules 1 to 3 mm. in diameter were seen just beneath the capsule and on the cut surface. The thymus gland and the pancreas each contained a firm white rounded nodule.

The ribs, the vertebrae and the pelvis showed foci of diffuse thickening, dark red, rather soft in consistency, the knife cutting through them with ease as though little calcium was left. The upper ribs and the alae iliorum showed the greatest change. The periosteum was diffusely elevated, no nodules being present. Sections presented an even dark red cellular surface with few bony spicules.

Microscopic Description.—Sections of the lungs revealed only patchy atelectasis and healed tubercles. The hepatic parenchyma had undergone extensive fatty change, and in one section it was replaced by a densely cellular mass made up of small round or oval cells with scanty cytoplasm and dense hyperchromatic nuclei embedded in a fine fibrillar matrix. In the spleen the malpighian corpuscles were indistinct and the pulp was prominent with swelling of the sinusoidal endothelium. The pancreatic acini were shrunken and degenerated, and in one section the

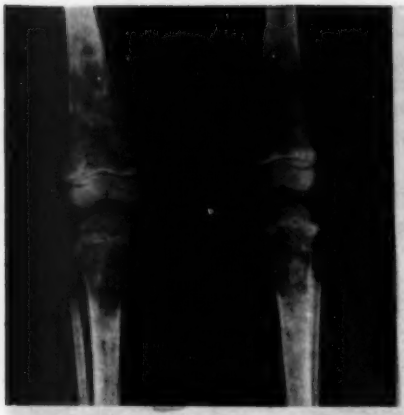

Fig. 1

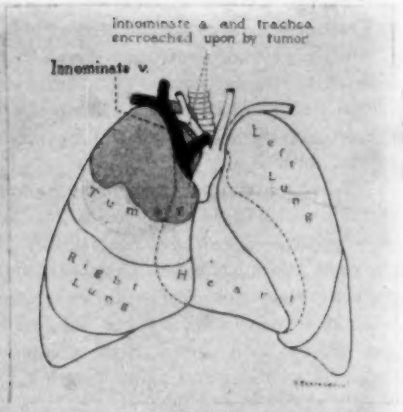

Fig. 2

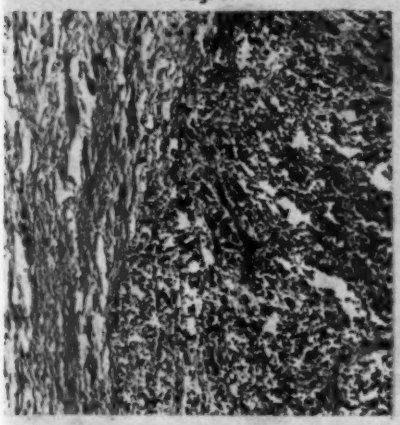

Fig. 3

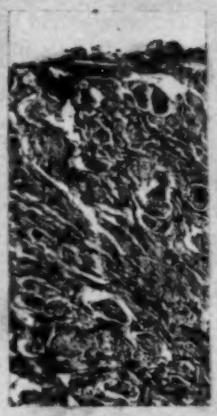

Fig. 4a

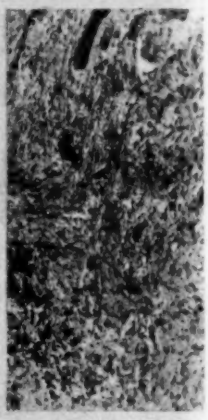

Fig. 4b

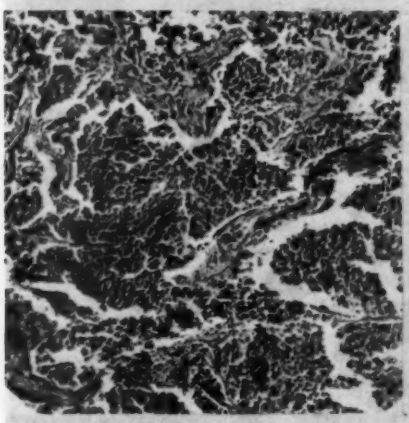

Fig. 5

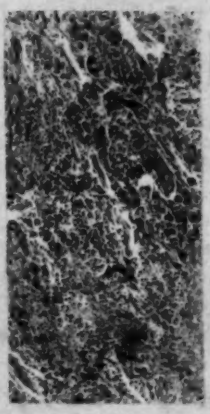

Fig. 6a

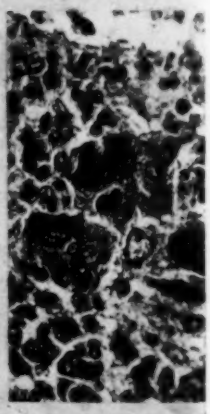

Fig. 6b

Figures 1 to 6b

(See legend on opposite page)

parenchyma was replaced by a partially encapsulated mass of cells quite similar to those described in the liver. Sections taken through the enlarged cervical nodes showed the same masses of cells as described in the liver.

Sections through the mediastinal tumor mass presented quite a variable picture. One section showed along one side a number of rather coarse bundles of nerve filaments. This area in which definite nerve trunks could be recognized merged gradually into an adjacent zone made up of irregular nests and clumps of small round or oval cells, all of which had dense hyperchromatic nuclei and many of which possessed delicate filamentous processes forming an irregular feltwork that tended to divide the cells into irregular nests of variable size and shape. In this same section there was another area in which a mantle of well defined neoplastic cells surrounded the blood vessels, while farther away from the vessels more degenerating tumor cells occurred. In such sections these areas of degeneration and necrotic tissue showed considerable calcification. In other sections there were considerable bundles of fine filaments, having much the appearance of neurofibrils. These could be traced for a considerable distance and extended irregularly through the tissue. No definite rosettes were seen. Frequently rather broad sheets of neurofibrillar tissue contained scattered neoplastic cells similar to those described, as well as more densely packed cellular foci. A moderate number of ganglion cells were also present in this neurofibrillar tissue.

Other areas in the tumor showed a different picture. One portion of the tissue was made up of small round or oval and stellate neoplastic-appearing cells, similar to those described in the foregoing paragraph, interspersed with broader and narrower bands of fibrillar structure showing irregular areas of hemorrhage and necrosis. In other places, however, the cells possessed a relatively abundant, finely granular cytoplasm and were elongated, fusiform or irregularly polyhedral. Considerable numbers of multinucleated giant cells were present, suggesting the structure of chromaffinoma. All transitions between this appearance and the more

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EXPLANATION OF FIGURES 1 TO 6b

Fig. 1.—Roentgenogram of the bones of both knees showing the metastases in the femurs and the tibias, especially near the knee joints.

Fig. 2.—A diagrammatic sketch of the heart and lungs showing the location and relations of the tumor.

Fig. 3.—Low power photomicrograph (× 61) showing clumps and clusters of sympathogonia invading a feltwork of neurofibrils containing degenerated ganglion cells. This was taken from the main tumor mass in the upper left side of the thorax.

Fig. 4a.—Lower power photomicrograph showing bundles of neurofibrils, taken from the main tumor mass. × 61.

Fig. 4b.—Lower power photomicrograph of an area in the main tumor mass showing ganglion cells embedded in a neurofibrillar stroma. × 61.

Fig. 5.—Low power photomicrograph of another portion of the tumor representing the structure of the bulk of the tumor sheets and masses of sympathicoblasts, some of which give the reactions of pheochromocytes. × 61.

Fig. 6a.—Low power photomicrograph of a field from the main tumor showing masses of pheochromocytes, with variation in cell shape and type, and secondary necrosis. Multinucleated giant cells are also seen. × 61.

Fig. 6b.—High power photomicrograph from an area similar to that shown in figure 6a. Note the large multinucleated giant cells with hyperchromatic nuclei. Some of these cells show a positive reaction with silver stains. × 290.

undifferentiated types of cells could be found. There was a tendency to separate the masses of cells into poorly defined lobules, partly separated from one another by delicate septums of connective tissue containing endothelium-lined spaces, some of which were filled with red cells. An affinity for silver salts was seen in the paragangliomatous cells (methods of Bielschowsky and of Wilder), and occasionally the cells of sections of tissue fixed in Zenker solution contained definite light yellow chromaffin granules.

Transverse sections through the ribs showed extensive replacement of the osseous tissue by neoplastic tissue of the neuroblastomatous type. No pronounced types of cells were recognized. They appeared undifferentiated and often showed a small bit of cytoplasm at one side of the nucleus or showed nuclei embedded in the fibrillar stroma. There were considerable congestion and hemorrhage with necrosis. The remnants of bone lay at the periphery of the rib.

Final Diagnosis.—Sympathogonioma (mixed neuroblastic and pheochromoblastic) with metastases to the skull, ribs, vertebrae, pelves, long bones, liver, lung, pancreas, thymus, upper thoracic wall and mediastinal cervical lymph nodes; acute dilatation of the heart; fatty change of the liver; acute splenitis; chronic focal pleurisy.

This tumor was unusual chiefly in that it was made of a widely diverse assortment of cells of sympathetic origin in all stages of differentiation from sympathogonia to adult ganglion cells and adult chromaffin cells. It obviously had its origin from the neurocytes of the sympathetic trunk in the upper thoracic region. The term "neuroblastoma" includes both sympathogonioma, composed of undifferentiated sympathetic cells, and the sympathicoblastoma, containing more differentiated elements. Differentiation was shown chiefly toward paraganglionic cells rather than toward neuroblasts, but in different sections either of these two cell types might be seen to be predominant. In a few areas nonmedullated nerve fibers and definite well differentiated ganglion cells could be recognized. Transitions could be seen between the primitive nerve cells and the chromaffin cells, like those of the adrenal medulla, some fields showing characteristic giant cells seen in the primary paraganglionic tumors of the medulla. Typical rosettes were not seen, but the fine fibrils were present often in bundles. Lewis and Geschickter [2] found rosettes in one third of the cases they studied, and Wahl [1] reported them in one half of the cases described in a previous paper. The metastases that were present were all of the embryonic neuroblastomatous type, the differentiated elements being located in the main tumor mass.

The location of a tumor of this type is another point of interest, since most sympathetic tumors have been found in the adrenal gland or the celiac region.

COMMENT

Unless mixed with undifferentiated cellular elements, the paraganglioma and the ganglioneuroma do not metastasize. Crile and Ball [13]

13. Crile, G. W., and Ball, R. P.: Surg., Gynec. & Obst. **48**:449, 1929.

stated that only cells of the most embryonic type are ever cancerous and that this type becomes increasingly benign as it reaches the adult stage. This is borne out by the age incidence for each of the three tumor groups, the average age for neuroblastoma being 2½ years (Blacklock [4]; Frew [14]; Reid [5]), that for ganglioneuroma 19 years in the 52 cases reviewed by Reid,[5] and that for paraganglioma the fifth decade, according to Lewis and Geschickter.[2] As a general rule, the younger the child the greater the degree of malignancy and the shorter the duration of life. With neuroblastoma the average length of life after onset was six months in the 40 cases of Lewis and Geschickter [2] and eight to nine weeks in Blacklock's [4] cases.

In neuroblastoma, widespread secondary involvement of bones—not only the skull, the ribs and the sternum but the long bones down to the hands and feet—is of frequent occurrence, and histologically the secondary growths are quite similar to primary growths with the exception that fibrils and rosettes are not usually seen. The mode of this spread has been the subject of much discussion. Frew [14] suggested a direct lymphatic spread from the primary neoplasm to the skull; Cohn (Blacklock [4]) stated that the greater vascularity of the ribs and of the skull of the infant accounts for the bony metastases but did not explain the pathway of implantation; Lehman [8] expressed the belief that the cells gain access to the greater circulation via a patent foramen ovale; others have assumed that the small cells could pass through the pulmonary capillaries to be disseminated by the general blood stream. Batson [15] in a recent publication provided a most plausible explanation for these bony metastases by demonstrating a hitherto little known circulation through the valveless veins in a great plexus about the vertebral column. By injection experiments he demonstrated that roentgen opaque material flows easily through this plexus, even at great distances from the sites of injection, directly to most of the bones of the body. The fact that the sympathetic ganglions and their gray and white rami communicantes lie in such close relationship to the vertebral bodies and thus in intimate association with the vertebral venous plexus makes this method of bony metastasis in the cancers of sympathetic origin seem quite likely.

SUMMARY

Of the three general types of sympathetic nerve tumors, various mixtures may be found in a given tumor, but the paragangliomatous elements tend more to be found in a pure state.

The thorax is not a frequent site of origin of these tumors; it has been reported as the primary site in 27 cases of ganglioneuroma, 13 of neuroblastoma and 2 of paraganglioma.

14. Frew, R. S.: Quart. J. Med. **4**:123, 1911.
15. Batson, O. V.: Ann. Surg. **113**:138, 1940.

The history and autopsy findings in the case of a 4 year old boy with a unique thoracic tumor bearing a mixture of all neurogenous elements with a preponderance of pheochrome cells are given. This tumor is of particular interest, as it not only showed undifferentiated neurocytes but illustrated their differentiation into ganglion cells, nerve fibrils and pheochromocytes, with an unusual accumulation of the latter; in fact, this tumor is unique in that it showed such a predominance of pheochromoblasts with the undiffereniated tissues, a finding not heretofore described in the thorax. It also showed cancerous parts, metastasizing widely and comprised of sympathogonia, and parts composed of both neoplastic differentiated nerve elements and pheochromocytes. Metastasis to bones by way of the paravertebral plexus of veins is suggested.

EFFECT OF MECHANICAL FORCE ON THE SKELETAL LESIONS IN ACUTE SCURVY IN GUINEA PIGS

RICHARD H. FOLLIS JR., M.D.
BALTIMORE

When one is considering a diagnosis of scurvy based on histologic changes at the ends of the growing bones of an infant or an experimental animal, there are certain criteria on which one leans heavily. Fractures of the "lattice," together with the presence of the *Trümmerfeldzone* (zone of detritus) and the *Gerüstmark* (framework marrow), make the presence of ascorbic acid deficiency a virtual certainty. Many who examine the bones of children at autopsies are probably loath to make a diagnosis of scurvy in the absence of these classic criteria. The fundamental disturbance in scurvy, however, is a failure of normal fibroblastic, osteoblastic and odontoblastic activity so that collagen, osteoid and dentin are not formed.[1] The relationship of this primary pathologic change to the final histologic picture is therefore not entirely clear. It has seemed fairly evident, however, that in scurvy, and in rickets as well, the mechanical factors of stress and strain must exert great influence on the final histologic picture. Park, Guild, Jackson and Bond [2] have commented on the importance of the effect of strain on the histologic changes encountered in the bones of scorbutic children. It appears, then, that if these mechanical effects could be prevented, the ensuing lesions in the bones might be modified. The present report deals with such an experimental study.

MATERIALS AND METHODS

Guinea pigs weighing 150 to 300 Gm. were fed a stock diet supplemented with carrots and ascorbic acid for a week or more. All sources of vitamin C were then excluded. A few days later a narrow plaster bandage was wound about one of the hindlegs. Beginning at the ankle, the winding was continued up to the thigh and then on up about the abdomen. This cast immobilized the leg almost completely, while the opposite one was allowed freedom of motion. The animals were killed at intervals of from ten to twenty days. The lower ends

From the Department of Pathology of the Johns Hopkins University School of Medicine.

1. (*a*) Wolbach, S. B., and Howe, P. R.: Arch. Path. **1**:1, 1926. (*b*) Wolbach, S. B.: Am. J. Path. **9**:689, 1933.

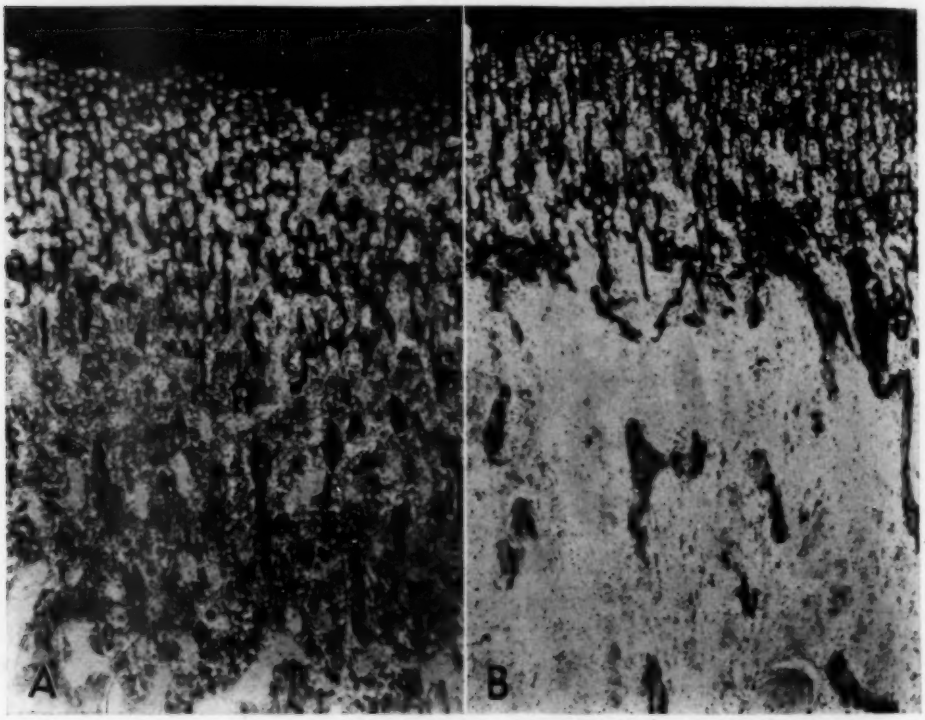
2. Park, E. A.; Guild, H. G.; Jackson, D., and Bond, M.: Arch. Dis. Childhood **10**:265, 1935.

of the femurs and the upper ends of the tibias were decalcified, embedded in paraffin or celloidin (a concentrated preparation of pyroxylin) and stained with hematoxylin and eosin.

EXPERIMENTAL RESULTS

The following description is a composite picture of the findings in a number of animals. The figure illustrates quite clearly the difference in the two extremities of each animal.

At the cartilage-shaft junction of the immobilized leg the cartilage appeared normal (*A* in figure). Beneath the zone of proliferative



A, cartilage-shaft junction of an immobilized leg of a guinea pig. Note the abnormally broad "lattice," which has no bone on it. Note also the marrow cells up to and between the columns of the "lattice." *B*, cartilage-shaft junction of the opposite leg of the same animal. Note the fractures of the "lattice" and the absence of marrow cells beneath it. Here there are connective tissue and red blood cells.

cartilage cells there was a broad "lattice" of calcified cartilaginous matrix, which was wider than one encounters normally. This matrix was arranged longitudinally and horizontally; the spaces thus formed indicated where cartilage cells had been destroyed. Blood vessels were found between the interstices of the matrix, and there were the usual numbers of connective tissue cells in such locations as well. It was

evident that invasion of the normal-appearing cartilage cell columns was taking place as usual. The abnormal feature, however, was that the "lattice" was not being destroyed. No osteoid or bone was found on the "lattice" until one reached its base, i. e., the place where the shaft began. Here there was a normal transition between the "lattice" and the bone. The absence of osteoid deposit on those portions of the "lattice" where osteoid should have been was the second pathologic feature. In the marrow spaces there was extensive erythropoietic and myeloid activity; the marrow cells came all the way up to the junction of "lattice" and shaft. No fractures of the "lattice" were observed except at the corners in a few animals. It was thought that these were due to incomplete immobilization of the knee joint in the cast. There was no proliferation of connective tissue cells nor was there any pink-staining "fibrin-like" material or hemorrhage.

In the animals whose legs had been allowed motion some rather marked differences were found (*B* in figure). The epiphysial cartilage was similar to that of the opposite leg. The "lattice" of calcified matrix in some animals was just as wide; in others it was narrower. This depended on the number and the severity of the fractures that were found. The points of fracture were characterized by an accumulation of pink-staining "fibrin-like" material, together with numerous osteoblastic cells, about the spicules of fractured "lattice." Giant cells were encountered about some of the broken remnants. There were hemorrhages as well. Marrow cells were not found at the cartilage-shaft junction, but there was a wide zone in which only connective tissue cells remained. Thus there emerged the classic picture of scurvy with fractures, *Trümmerfeldzone* and *Gerüstmark*.

COMMENT

It seems clear that when one eliminates the usual stresses and strains that accompany motion of the extremities, the histologic picture of the skeleton in ascorbic acid deficiency is greatly altered. Such a study indicates that all the usual criteria which one calls on in establishing a diagnosis of scurvy are entirely secondary to the initial cessation of osteoblastic activity as indicated by a failure to destroy the calcified cartilaginous matrix and to form osteoid.

There are several points that might be stressed. The pink-staining "fibrin-like" material that appears about fractures has been interpreted by students of scurvy in various ways. Aschoff and Koch [3] thought it was fibrin, while Höjer [4] decided it was bone of an inferior type. Wol-

3. Aschoff, L., and Koch, W.: Skorbut, Eine pathologisch-anatomische Studie, Jena, Gustav Fischer, 1919.

4. Höjer, J. A.: Acta pædiat. (supp.) **3**:8, 1924.

bach and Howe [1a] thought it "had as its basis a product of the cells of the *Gerüstmark,* probably liquid until added to by other materials from the blood plasma or cartilage matrix resorption." The failure to observe this material in the immobilized bones would serve to indicate that its appearance is secondary to the fractures and possible rupture of capillaries and that it does not represent a defective product elaborated by the osteoblasts as Wolbach and Howe [1a] suggested, unless these cells are stimulated to an attempt at healing.

In this study of acute conditions no disturbance in the invasion of the cartilage cell columns by capillaries was observed. Wolbach's [1b] experiments would indicate that in the scorbutic state there is a failure of endothelial cells to form capillaries just as there is a failure of connective tissue cells to form intercellular substances. Experiments similar to those reported here but of a more chronic nature might bring out this defect.

What the stimulus for the disappearance of the myeloid elements and the appearance of the *Gerüstmark* may be is difficult to decide. The occurrence of the fractures with the subsequent hemorrhage and connective tissue proliferation coincides with the disappearance of these cells from this area. Changes in the environment, such as anoxemia or differences in p_H, may be important.

These experiments seem to indicate that one might be able to diagnose scurvy in children and animals on the basis of a persistent "lattice" and lack of bone formation. My associates and I will discuss this question in another place and can say now only that a positive diagnosis on such a basis is in our experience well nigh an impossibility.

It should also be pointed out that a persistent "lattice" with little or no bone deposited on it is not specific for ascorbic acid deficiency. In congenital syphilis similar changes are encountered.[5]

SUMMARY

A study has been made of the effect of immobilizing an extremity on the ensuing histologic picture of experimental scurvy in guinea pigs. It was found that the classic picture, with fractures, *Trümmerfeldzone* and *Gerüstmark,* failed to appear. This indicates that these are secondary to the failure of bone to be deposited on the delicate calcified cartilaginous matrix.

5. Park, E. A.; Jackson, D.; Goodwin, T. C., and Kajdi, L.: J. Pediat. **3**:265, 1933.

HISTOLOGIC OBSERVATIONS ON THE CHANGES IN THE BRAIN IN ROCKY MOUNTAIN SPOTTED FEVER

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CINCINNATI

A histologic study of a victim of Rocky Mountain spotted fever is presented in which particular attention was paid to a special pericapillary cellular reaction.

A 67 year old white woman was admitted to the Cincinnati General Hospital Jan. 24, 1941. About three weeks previously she and her two grandchildren visited in Kentucky. Two weeks later she became ill with nausea, vomiting and diarrhea. About the same time the two grandchildren became ill. A few days later the patient, as well as the children, presented a rash which appeared on the ankles and then spread rapidly over the rest of the body. For the next five days the patient was delirious and had a high fever.

On examination the patient had a generalized macular hemorrhagic eruption over the entire body except the face. The blood pressure was 94 systolic and 60 diastolic. Respiration was labored and rapid, and the heart sounds were rapid and feeble. The temperature was 103 F. and the patient was delirious. She was hypersensitive to touch. There was rigidity of the neck, with hyperactive tendon reflexes and bilateral extensor plantar responses. The temperature rose steadily and finally reached 106.8 F. The patient died after twenty hours in the hospital. The red blood cell count was 6,160,000; the white cell count, 10,000, with 82 per cent polymorphonuclear leukocytes. The initial reading of the cerebrospinal fluid pressure was 110 mm. of water. The fluid contained 11 lymphocytes and 21 red blood cells per cubic millimeter. The result of the Pandy test was normal. The Wassermann reaction of the blood was negative, and the blood cultures remained sterile. The Weil-Felix reaction in the blood was positive.

The gross pathologic abnormalities were diffuse pulmonary edema and congestion, congestion of the liver, the spleen, the kidneys, the fundus of the stomach, the small and the large bowel and the meninges, and petechial hemorrhages of the skin, the liver, the kidneys and the mucosa of the cecum.

The following areas of the brain were removed for microscopic examination: the right basal ganglions with cortex from the sylvian fossa and the hippocampal gyri, several other areas of the cortex and portions of the pons and the medulla.

The histologic examination revealed miliary granulomas and capillary changes. These lesions varied in number and in degree in different regions of the brain.

The most striking manifestatation of the pathologic process was the presence of small focal lesions in the form of miliary granulomas widely scattered throughout the brain substance. The granulomas as seen in cross section were generally circular or ovoid and were composed of compact accumulations of large irregular

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polygonal or oblong cells (fig. 1 *A*). The cells usually varied considerably in size and shape. The cytoplasm stained lightly and homogeneously except occasionally, when it appeared coarsely granular. The cell nuclei were round, oval or oblong and usually poor in chromatin. The central part of some of the

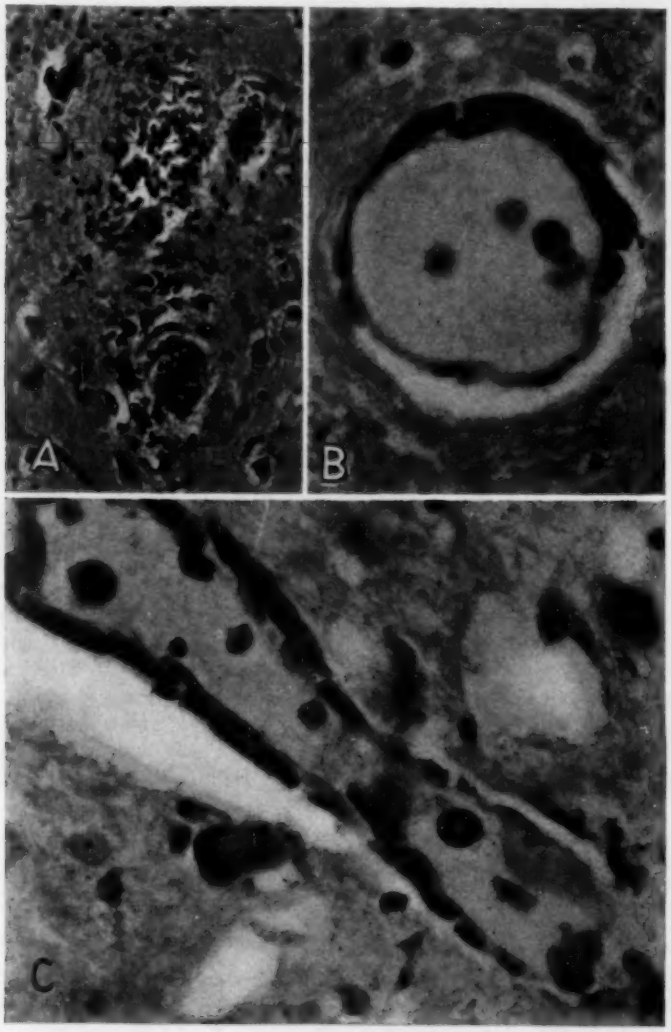

Fig. 1.—*A*, miliary granuloma formed by compact accumulation of irregular polygonal and oblong cells. Cresyl violet; × 135. *B*, pericapillary proliferation of a small number of large mononuclear cells. Note the normal appearance of the endothelial cells. Cresyl violet; × 165. *C*, pericapillary cell proliferation. Cresyl violet; × 165.

granulomas appeared edematous, and the cells were degenerated so that their form and structure were not recognizable. Inflammatory phenomena and hemorrhages were not found in the granulomas or in the surrounding brain tissue.

The majority of the granulomas contained capillaries. Only a few were avascular. It appeared probable that an associated vessel might have been found in each granuloma if serial sections had been made. The endothelial layer of the capillary was normal except for a moderate degree of hyperplasia. There was marked cell proliferation in the adventitia, which was infiltrated by large mononuclear cell elements that in their structure resembled those of the neighboring granuloma cells. There seemed to be transitions from the cells derived from the capillary wall to the granuloma cells.

The Cajal gold sublimate stain revealed only an occasional astrocyte among the other cells of the granuloma. This cell probably belonged to the preexisting glia. There appeared to be no relation between it and the granuloma cells. About the margins of some of the granulomas there was a slight accumulation of hyperplastic microglia cells. There was no evidence of transition from these cells to the granuloma elements.

Where granulomas were present, nerve cells, myelin sheaths and nerve fibrils had practically disappeared. In the tissue surrounding the granulomas the nerve cells were fairly well preserved.

The extensive and characteristic lesions of the capillaries of the brain deserve attention. The earliest change consisted of a pericapillary proliferation of a small number of large mononuclear polygonal cells around a limited sector of a capillary (fig. 1 *A* and *B*). These cells, slightly hypertrophied, contained vesicular nuclei and resembled the so-called Rouget cells lining the capillary wall. More extensive and presumably more advanced lesions affected the entire circumference of the capillary, so that there was concentric thickening of the walls of the vessel due to an accumulation of large numbers of mononuclear cells (fig 2 *B* and *C*). No lymphocytes or plasma cells were present. The endothelial cells which line the capillary lumens were not recognizable in this later stage.

In the longitudinal sections of some capillaries it was noted that the mononuclear cells originated from the adventitial capillary tunic and infiltrated the surrounding nerve tissue, forming a small granuloma (fig. 2 *A*). The majority of the diffusely scattered smaller aggregations of cells, which evidently represented the early stage of granuloma formation, were formed around capillaries. The proliferation of the capillary wall could be regarded as their origin (fig. 2 *A*). Many of the granulomas revealed early signs of dissolution and necrosis, which destroyed the cells and the capillary wall from which they originated (fig. 2 *B*). In the more advanced lesions in which the wall of the blood vessel as well as the granuloma cells were degenerated, the structure of the granuloma and its connection with the capillary could not be recognized. No noteworthy changes were present in the arteries or in the veins of the brain. The majority of the smaller veins and capillaries revealed signs of dilation with passive hyperemia, and occasionally they were surrounded by small perivascular hemorrhages.

In scarlet red preparations the ganglion cells throughout the brain cortex exhibited slight signs of fatty degeneration. Granules of fat were present in the adventitia of the small arteries. No trace of inflammation was found in the meninges, the cortex or the white matter. No areas of primary demyelination were found, and only here and there was there some rarefaction of the myelin network in the main pathways. In some areas in which the granulomatous formation was more marked, both progressive and regressive glial changes were present. The degenerative changes consisted in swelling of the cell body and tumefaction of the processes, which were undergoing gradual disintegration. The

progressive changes were a slight increase in the number of microgliocytes, especially pronounced in the vicinity of the granuloma. No special search for microorganisms (rickettsias) was made, though minute basophilic inclusions were occasionally found in the media and the adventitia of some arteries.

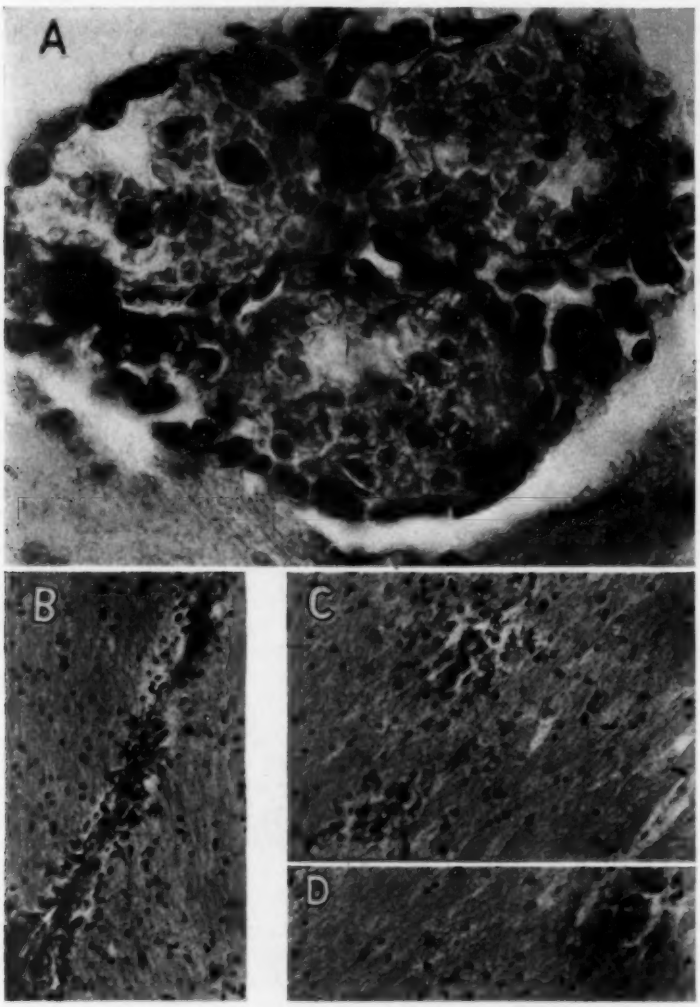

Fig. 2.—*A*, advanced cell proliferation around the capillaries with concentric thickening of the wall. Cresyl violet; × 135. *B*, longitudinal section of a capillary which is surrounded by a large mass of mononuclear cells from the adventitial tunic of the blood vessel. These cells infiltrate the surrounding nerve tissue and give rise to granuloma. Cresyl violet; × 135. *C*, and *D*, small perivascular granulomas with early signs of dissolution and necrosis of the granuloma cells. Cresyl violet; × 135.

In summary it appears that the most constant and uniform lesion in the brain was the widely disseminated granuloma formation. In the majority of instances the granuloma was in direct contact with a capillary, from the wall of which its cells appeared to be derived. In some areas, however, the cellular agglomeration appeared avascular and showed no obvious relationship to a blood vessel. Probably in these areas necrosis of the vessel walls had occurred.

The cerebral histologic changes of Rocky Mountain spotted fever in man have been reported only casually. Most descriptions have dealt with changes observed in the central nervous system as observed in animals. In the majority of 20 cases of Rocky Mountain spotted fever commented on by Wolbach [1] the central nervous system had been reported as normal. Wolbach's study demonstrated the remarkable specificity of the micro-organism (rickettsia) of Rocky Mountain spotted fever for the peripheral circulation. Wolbach recorded fully the lesions in the various organs (except the central nervous system) in man and experimental animals. He noted that "the vascular lesions are at first essentially proliferative (endothelium) followed by necrosis of small groups of cells." The character and evolution of the rash with the cutaneous sequelae (necrosis or gangrene) were explained by the lesions of the blood vessels.

Similar observations were earlier recorded by Le Count,[2] in the skin, the liver, the kidney, the spleen and the adrenal glands. Lillie [3] described the findings in the central nervous system as determined in a study of 5 autopsy records. Three different types of brain lesions were recorded: "Those involving vessels and their sheaths, focal proliferative lesions in the brain substance and focal necroses." Similar vascular and focal lesions were present in cases reported by Pinkerton and Maxcy [4] and Harris.[5] Changes of the same kind as those seen in the brain of man have been produced in animals infected with Rocky Mountain spotted fever (Lillie, Dyer and Topping [6]). Hassin [7] described mild inflammatory and degenerative changes in the brain in a fatal case of Rocky Mountain spotted fever. The histologic findings were classified by him as nonsuppurative meningoencephalitis and designated as being "not typical of any particular form of encephalitis."

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7. Hassin, G. B.: Arch. Neurol. & Psychiat. **44**:1290, 1940.

COMMENT

It seems proper to attempt to correlate the cerebral findings in this case with those described in the literature. The formation of the miliary granulomas seems to be a constant and characteristic finding in cases of Rocky Mountain spotted fever. Lillie [3] described the granulomas as accumulations of "leptochromic glia nuclei in single rows along the sheaths of vessels." Hassin [7] noted that the cells of the granulomas were "not fibroblasts or microgliocytes but probably oligodendrocytes or glia nuclei." The same type of lesion has been repeatedly reported in cases of typhus fever; it has been observed in cases of epidemic encephalitis, toxoplasmic encephalitis and Borna disease and in cases of encephalitis associated with trichinosis and that associated with malignant endocarditis. In some forms of encephalitis (Trichina and Toxoplasma) the miliary granulomas contain parasites. These lesions are probably a manifestation of a local tissue reaction to the presence of an infectious invader.[8]

There are several bits of evidence that indicate the miliary granulomas are not glial in origin: their development around blood vessels, the constant presence in them of large mononuclear cell elements which are not stainable with specific methods for staining glia and the resemblance of these cells to the large mononuclear cells found in the circumference of the capillary and presumably derived from the adventitial tunic of the vessel wall. It was possible to make a clearer interpretation than heretofore of the nature of the pericapillary cellular proliferation in the case under discussion because of the absence of perivascular inflammatory reaction.

It seems proper to conclude that the granuloma cells are mesodermal in origin and that probably they are derived from the adventitial tunic of the capillary.

In support of the mesodermal origin of such cells is the work of Wolf and Cowen,[9] who described miliary granulomas in toxoplasmic encephalitis as follows: "In most cases the granulomas surrounded or were in contact with a small blood vessel from the wall of which its epitheloid cells appeared to be derived." Harris found that "in addition to the true perivascular cellular infiltration many of the arteries within the brain tissue show an accumulation of monocytes in the stroma which accompanies them in their course." Wolbach [1] mentioned that "the earliest lesion in the vessels is a collection of large mononuclear phagocytic cells (endothelial cells) over an area of swollen and degenerated endothelium of the intima." On the other hand, in cases

8. Hassin, G. B., and Diamond, F. B.: Arch. Neurol. & Psychiat. **15**:34, 1926. Hassin.[7]

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of granuloma formation in typhus fever the origin of the granulomas has been ascribed to necrosis of the endothelium of the blood vessels, which was thought to be the primary phenomenon (Jahrisch [10]; Herzog [11]; Bauer [12]; Ceelen [13]; Gross [14]).

SUMMARY

The histologic observations in a fatal case of Rocky Mountain spotted fever are reported. The changes consisted of a proliferative cellular reaction of the capillary wall and formation of scattered miliary granulomas. The granulomas and the proliferative reaction, made up of large mononuclear cells, appeared to be derived from the capillary adventitia and therefore to be of mesodermal origin. The degenerative phenomena consisted of lesions of the ganglion cells combined with a mild focal microglial proliferation in the neighborhood of the granulomas.

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11. Herzog, G.: Centralbl. f. allg. Path. u. path. Anat. **29**:97, 1918.
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Case Reports

SEMINOMA DEVELOPING IN AN UNDEVELOPED GENITAL ANLAGE

H. Gideon Wells, M.D., Chicago

Twenty-five years ago I performed a necropsy in a case the like of which I had not seen or heard of previously. Since then I have waited in vain to see a report of a similar case, but none has appeared. Therefore it seems to be about time to put the case on record.

REPORT OF A CASE

A 47 year old press feeder, came to the service of Dr. Wilber E. Post at the Cook County Hospital, Chicago, on Feb. 13, 1917 and died on March 10, 1917. He complained of loss of weight and weakness which had prevented him from doing any work for five months. He had a pain in the left side in the posterior axillary line at the level of the lowest rib. He did not cough, there was no edema, he had never been married and denied that he had ever had a venereal disease. In his reactions and behavior he was decidedly infantile. Hypospadias was present, there was no right testicle in the scrotum and the left testicle was decidedly atrophic. The lower border of the liver was 3 fingerbreadths below the costal margin and overlay a large retroperitoneal mass. There was an increased prominence of the hypogastric and epigastric veins. Death occurred from terminal hypostatic bronchopneumonia.

Necropsy revealed the following significant findings: The body was that of a very small (5 feet [152.5 cm.] tall), poorly nourished and poorly developed man, looking somewhat younger than the stated age. The beard, mustache, axillary and pubic hair were very sparse. The face appeared childish. The superficial lymph nodes were not palpable. There was noticeable exophthalmos. The right testicle was not present in the scrotum, and there was no scar to indicate an operative removal. The left testicle was present in the scrotum and about one third the normal size. The penis was only 2 cm. long, and the urethra, discharging a bloody urine, opened between the base of the penis and the scrotum; there was no urethra whatever in the penis.

When the abdominal cavity was opened, there was found no undescended testicle at any site, no right spermatic cord, no right seminal vesicle. The prostate was about half the normal size, and the right half was merely a fleshy mass. The left seminal vesicle was present in the form of a large hollow sac, and the left testicle was reduced to a small mass, 1.5 cm. in diameter, with a small epididymis.

A large tumor mass was located retroperitoneally and nearly symmetrically, although a little larger portion was on the left side. The stomach was pushed to the left and was adherent to the tumor mass, the pylorus being stretched out so that it resembled the duodenum. The tumor mass lifted up the root of the mesentery and ascended up through the root of the diaphragm to the level of the seventh dorsal vertebra, the portion in the thoracic cavity extending 10 cm. above the diaphragm and being 15 cm. in breadth. The entire mass was 35 cm. long,

From the Department of Pathology of the University of Chicago.

25 cm. wide at its widest part and 20 cm. thick. On the anterior surface was a groove containing the portal vein, which evidently was not greatly compressed, since there was no ascites. The tumor tissue was adherent to the vertebral fascia and infiltrated the perivertebral tissues and the bodies of the vertebrae themselves. It consisted of large lobulated masses of pinkish white tissue without evident areas of necrosis, its consistency being somewhat firmer than normal liver tissue, and the weight was 2,800 Gm. The aorta and the vena cava ran through the mass but were not occluded by it.

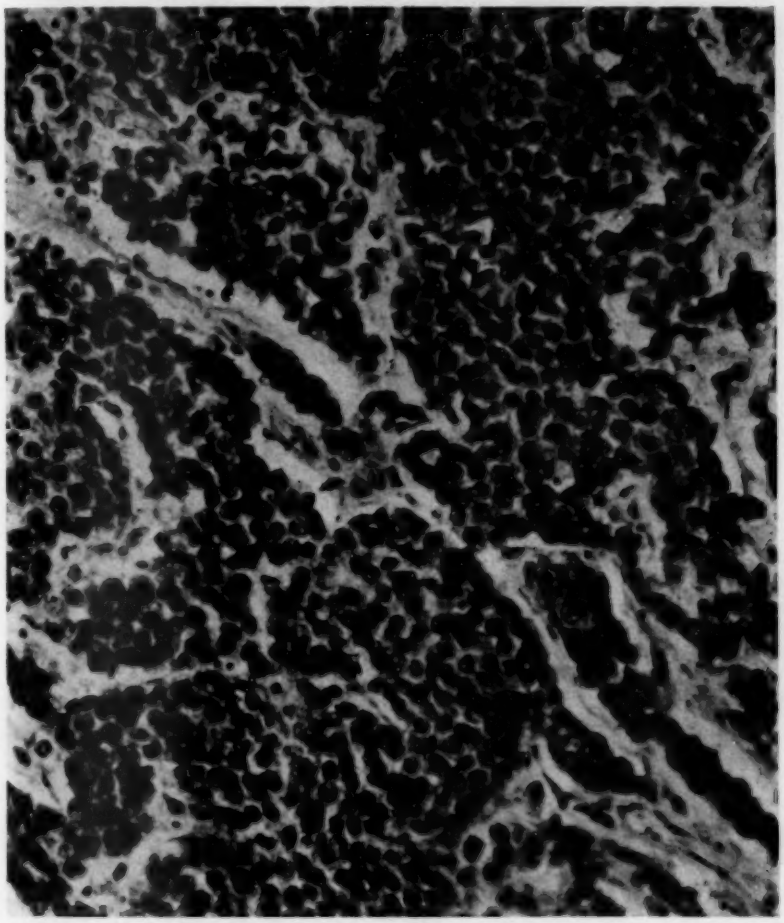

Fig. 1.—Section of the primary tumor (× 235) showing the seminoma-like structure.

The left kidney was not adherent or involved with the tumor in any way and appeared practically normal. The right kidney was forced downward and spread out like a capsule over a mass of tumor tissue entering the hilus but not infiltrating the kidney tissue. The urinary bladder was distended but appeared normal. The right adrenal was adherent to the tumor but not involved. The left adrenal was flattened and spread over a nodule of tumor tissue but not infiltrated. The pancreas

was spread out flat and thin over the tumor but was not infiltrated. There were no remote metastases, but three lymph nodes about the base of the bladder were slightly enlarged.

There was a general small size of the viscera (heart, 150 Gm.; liver, 800 Gm.; spleen, 80 Gm.). The gallbladder was packed with 250 gallstones. The left lung showed hypostatic bronchopneumonia.

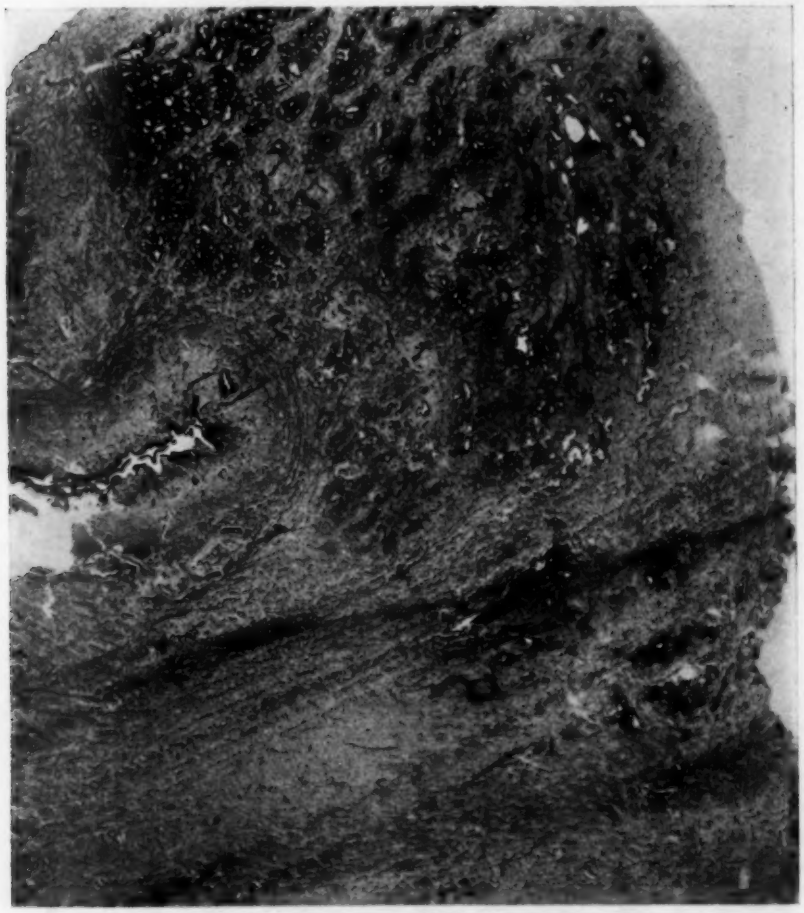

Fig. 2.—Section of the prostate (× 10) showing the presence of undeveloped tubules in the left half and the absence of tubules in the right half.

Microscopically, the tumor was a large-celled alveolar growth (fig. 1), resembling typical testicle tumors, with many atypical mitotic figures—in structure a seminoma. The pelvic lymph nodes and the vertebrae adjacent to the tumor were extensively invaded by the same sort of growth. The left testicle showed a condition of extreme atrophy with hyalinization of the basement membrane of the seminiferous tubules and no germinal epithelium present at all; the interstitial

tissue contained but few cells of Leydig. The left epididymis was infantile in character. Most interesting was the prostate, for in the right half were no tubules whatever, only nonstriated muscle, while the left half had a few tubules of infantile character (fig. 2). Obviously, the entire right genital anlage had failed to develop, while the left had developed but partially. Apparently, the undeveloped genital anlage had remained quiescent for forty odd years and then developed as seminoma, as retained abdominal testes are wont to do.

Dr. Judson B. Gilbert, of Schenectady, N. Y., who has made a most thorough investigation of cancer in retained testicles,[1] informs me that he knows of no case similar to this in which the whole right genital anlage has failed to develop and then become a cancer.

SUMMARY

A case is reported of complete failure of the right genital anlage to develop, associated with immaturity of the left genital anlage. At the age of 47 the patient died with a retroperitoneal seminoma, apparently arising in the rest of undeveloped right genital anlage.

University of Chicago.

1. Gilbert, J. B., and Hamilton, J. B.: Surg., Gynec. & Obst. **71**:731, 1940.

UNIQUE CELL REST IN A UTERINE FIBROID

AUGUSTIN R. PEALE, M.D., AND LAWRENCE W. SMITH, M.D., PHILADELPHIA

A case is presented which is of unusual pathologic interest because of a rare and fascinating lesion that was found incidentally on microscopic study of the surgically removed uterus. The rarity would seem to be indisputable, for we have been unable to find in the literature any description of a comparable lesion in this particular situation, nor have we ever encountered a similar picture in any of our fairly extensive surgical or autopsy material. Its fascination lies in the attempt to account for its occurrence and localization on an embryologic basis.

REPORT OF A CASE

A white woman of 40 years, married, was admitted to Temple University Hospital as a private patient of Dr. Harry A. Duncan, who made this brief clinical abstract available.

The patient had complained of progressive fatigability associated with a brownish vaginal discharge, which had been present for about a year. There had been no frank vaginal bleeding nor any other symptom immediately referable to the genital tract. The menstrual cycle had been regular, every twenty-eight days, the bleeding phase lasting for seven days. The last menstrual period had been approximately two weeks prior to admission.

Seventeen years previously the patient had undergone appendectomy, and twelve years before, the left fallopian tube was removed because of tubal pregnancy. Otherwise she had never had any serious illness. She has one child, 15 years of age, living and well.

Examination revealed nothing other than moderate enlargement of the uterus, thought to be due to multiple fibroids.

Abdominal hysterectomy, right salpingectomy and bilateral ovariectomy were performed following exploratory laparotomy. She made an uneventful postoperative recovery and was discharged cured.

Gross Examination of Specimen.—The specimen consisted of a uterus with the cervix attached, the right fallopian tube and the corresponding ovary. The uterus and cervix together measured 11 by 9 by 5 cm. opened. The contour of the uterus was distorted by several fibroids, the largest of which measured 4.5 cm. in diameter. This was subserous in location and situated on the lateral anterior wall of the fundus in close proximity to the left cornu. On the serosal surface there were several smaller similar-appearing masses, measuring about 3 to 5 mm. in diameter. On this same side there was a discolored soft spherical mass tightly adherent to the lateral aspect of the fundus of the uterus, which measured 4 cm. in diameter. This mass was multicystic; many of the cysts were filled with a thin chocolate-colored fluid material. The cyst linings were smooth. Grossly this tissue resembled ovary. There was no corresponding tube, as it had been removed for ectopic pregnancy at a previous operation, as specified in the case report. The cervix was firm and revealed small nabothian cysts. The endometrium was pale, velvety and smooth except for a submucous fibroid at the fundus. The

From the Department of Pathology of the Temple University Hospital and School of Medicine.

right tube was grossly healthy. The corresponding ovary had an aberrant location, being situated at the midportion of the tube, to which it was tightly adherent. Cut sections showed moderate sclerosis, a small follicular cyst and a small corpus luteum.

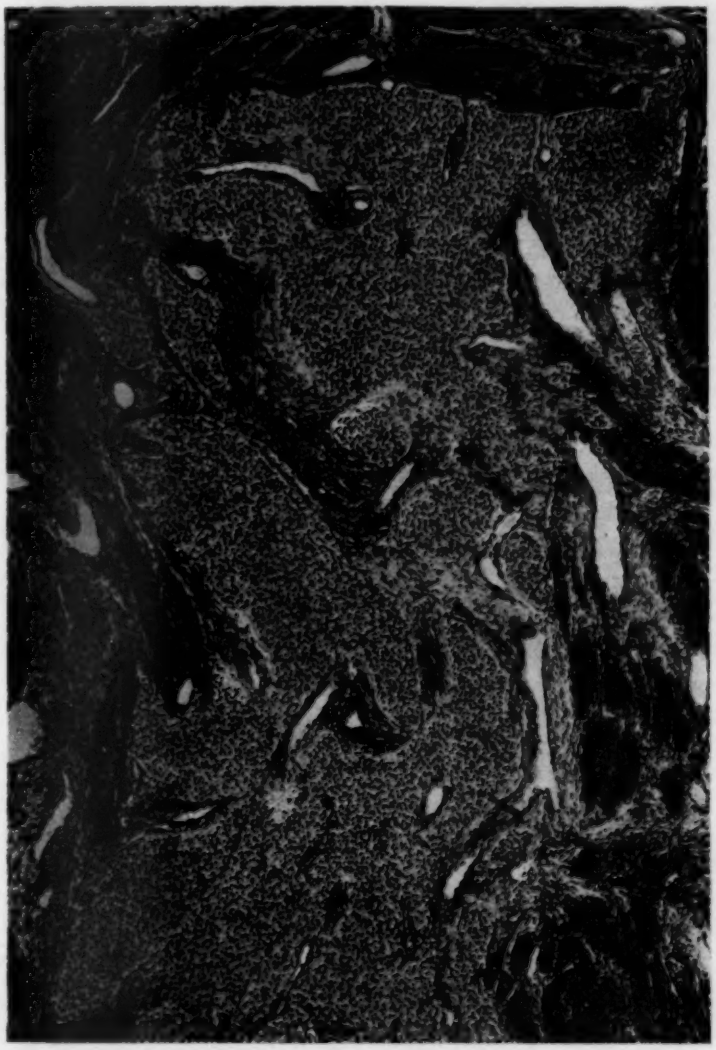

Fig. 1.—Appearance of the cell rest under low power.

Microscopic Study.—There was an early premenstrual endometrium. The tube showed nothing of histologic significance. The right ovary was sclerotic and confirmed the gross findings of a small follicular cyst and of a small corpus luteum. The cystic mass described on the left side of the uterus proved to be ovarian tissue in which there were several cysts; the linings of the majority of these were

replaced by mononuclear phagocytes distended with old blood pigment, although one was covered by a layer of endometrial tissue.

Sections from the large subserous fibroid revealed that scattered throughout the fibromuscular tissue background there were nests and islands of cells with

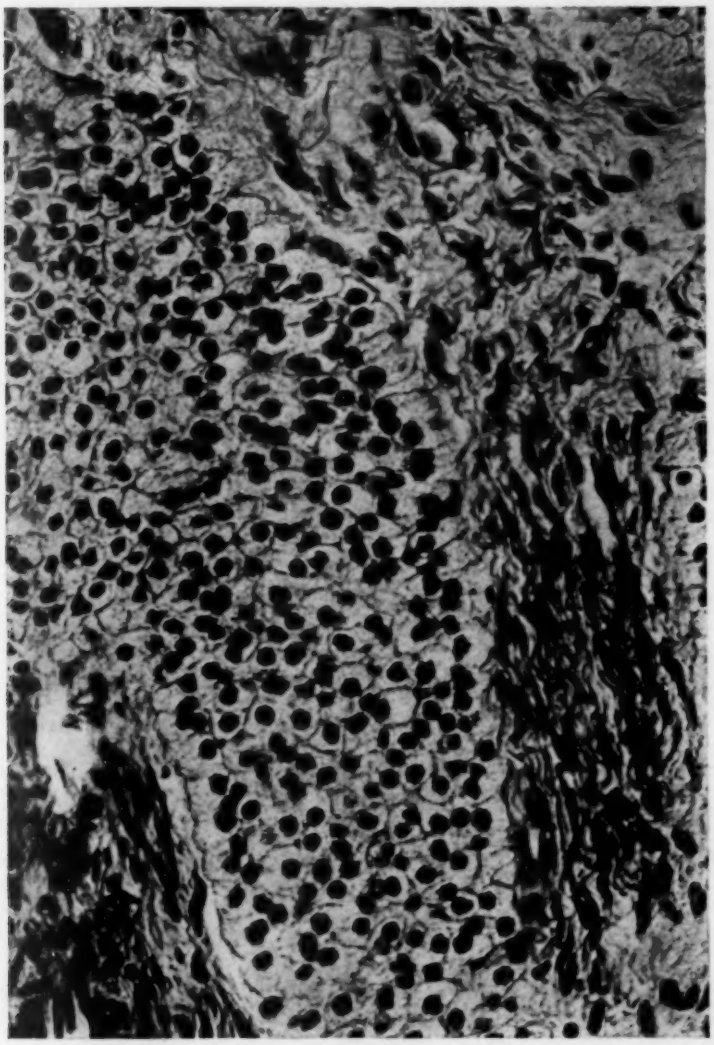

Fig. 2.—High power magnification of the cell rest.

clear cytoplasm and centrally placed, deep staining round nuclei. The peripheral cells in these nests and islands had a palisaded columnar appearance with the nuclei basally placed. There was neither cystic degeneration nor calcification. On cytologic grounds we concluded that these cells represented embryonal remnants and considered the possibility that they had their origin either in rests of adrenal cortex or in Walthard rests.

COMMENT

Islands of adrenal cortex have been reported at the hilus of the ovary, and similar rests have been described even in the broad ligament.[1] So it is conceivable that they may be found in the serosa or the subserosa of the uterus. We were unable to do a fat stain, which would have been most helpful in accurately classifying these cells, because despite the fact that the specimen had been saved in solution of formaldehyde, almost serial section of the fibroid and of other areas throughout the uterus failed to reveal any similar-appearing cells. This would seem to indicate that these rests of cells were limited to a very small area.

In explaining the picture on the basis that the cells were derived from Walthard rests we must conjecture that these cells were present on the surface of the fundus uteri or that they were present in the broad ligament and that the tumor arose from the latter region with extension into the subserosa of the uterus. Such a theory is not too far fetched, because Walthard rests have been reported as low as the broad ligament, although they are more frequently and more commonly found in the ovary.[2] Masson and Van Gieson stains failed to be of any help to us in arriving at a definite conclusion. If this concept is true, we are dealing with a Brenner tumor which apparently arose in the broad ligament and grew into the subserosa of the uterus to appear grossly as a subserous fibroid.

The slides were submitted to several gynecologic pathologists for an expression of opinion regarding the nature of these cells. No unanimity of opinion was obtained, both the adrenal rest and the Walthard cell rest theories being supported. One pathologist finally concluded that the picture probably represented an unusual cancerous phenomenon in a fibroid. To the latter view we cannot subscribe.

SUMMARY

A case in which peculiar unidentified rests of cells were found in what grossly appeared to be a subserous uterine fibroid is reported. We offer two possible explanations for their origin, namely, adrenal cortical cell inclusions or Walthard cell rests.

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OBSTRUCTIVE APPENDICITIS CAUSED BY A SPROUTING SEED

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AND
MAJOR WARNER F. BOWERS
Medical Corps, Army of the United States

In the most ancient writings on appendicitis [1] foreign bodies appear to be the usual cause of the disease. Mestivier, a French surgeon, performed the first modern operation for appendical abscess in 1759, and the subsequent autopsy showed that fatal peritonitis had been caused by a pin perforating the wall of the appendix. During the next fifty years four necropsies were reported in the French literature, and in each case a foreign body had perforated the appendical wall. Foreign bodies undoubtedly are found as frequently today as formerly, but owing to the large number of appendectomies done, the incidence appears to be relatively smaller. The following case seems to be of sufficient interest to warrant a report and short discussion.

REPORT OF A CASE

A 22 year old white soldier was admitted to the Station Hospital, Fort Leonard Wood, Mo., at 1:30 a. m., Sept. 20, 1941, complaining of pain in the right lower abdominal quadrant of four hours' duration, associated with nausea, vomiting and a chill. At 7 p. m., three hours before the onset, he had received 1 cc. of typhoid vaccine (first injection) and 1 cc. of tetanus toxoid (second injection). At 10 p. m. he experienced a sudden pain in the right lower abdominal quadrant, and shortly thereafter, became nauseated and vomited. About 10:30 p. m. he had a chill and was seen by the dispensary medical officer who sent the patient to the hospital. The past history was significant in that there had been intermittent attacks of pain in the right lower abdominal quadrant several times a year for the past ten years. In August 1940 he had a severe attack, and operation was advised by his physician but was opposed by his family. After eight days in bed he recovered spontaneously. One month before admission a similar attack subsided in two days. On entry the temperature was 104 F., the pulse rate 120 and the respirations 20 per minute. There was slight generalized abdominal tenderness without point or rebound tenderness or muscle guard. The urinalysis disclosed no abnormalities. A blood count showed the hemoglobin content 100 per cent, erythrocytes 5,030,000 and leukocytes 15,300, with 90 per cent polymorphonuclear neutrophils, 7 per cent lymphocytes, 1 per cent basophils, 1 per cent eosinophils and 1 per cent monocytes. The patient was observed carefully during the night, and in the morning the temperature was 99 F., the pulse rate 94 and the respirations 22 per

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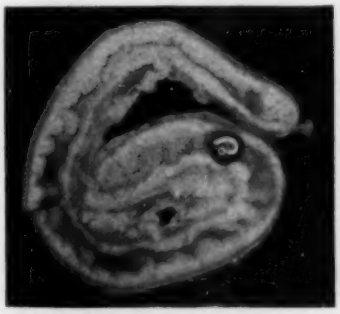
From the Surgical Service of Col. Millard F. Arbuckle, Medical Corps, United States Army, Station Hospital.

1. Collins, D. C.: Ann. Surg. **94**:179, 1931.

minute. About 4 p. m. he had another chill, and the temperature rose to 101.2 F. An increase in abdominal pain accompanied this. At this time a blood count showed 26,500 leukocytes with 94 per cent polymorphonuclear neutrophils and 6 per cent lymphocytes. Shortly thereafter there was localization of the pain in the right lower abdominal quadrant with development of muscle guard, rebound tenderness and point tenderness over McBurney's area. At 7 p. m., with the patient under spinal anesthesia induced with 150 mg. of procaine hydrochloride, the peritoneal cavity was opened and the appendix was found lying over the brim of the pelvis. The surface vessels were congested, and the terminal centimeter of the appendix was firm and tense. The appendix was removed, and the stump was ligated and inverted. The temperature fell to 98.2 F. in the first six hours, and the highest postoperative temperature was 99 F. on the second day. A leukocyte count on the third day was 32,350, with 95 per cent polymorphonuclear neutrophils, 34 per cent lymphocytes and 2 per cent monocytes. On the fifth day the patient was out of bed and the skin superficially was well healed. The total leukocyte count at this time was 5,250 with a normal differential count. The further course in the hospital was uneventful, and the patient was discharged on the fourteenth postoperative day.



This photograph shows the appendical lumen obstructed by a sprouting seed. Note that the lumen distal to the point of obstruction is distended and that the rugations have disappeared. The wall is noticeably thinned. Proximal to the seed the lumen and wall are normal. Microscopic evidences of inflammation are limited to the area distal to the obstruction.

The appendix was 6 cm. long and 6 mm. in diameter, dilated to 7 mm. in diameter in the terminal 1.5 cm. The subserosal capillaries were congested, but there was no exudate. On longitudinal section the lumen was of normal caliber and the mucosa smooth to a point 1.8 cm. from the distal end, where a small flat seed was present. Just beyond this the lumen was obstructed by a round, moderately firm brown body, 2 by 2 by 2.5 mm. On section this object showed a dark brown cortical portion and a central portion occupied by a hypocotyl and root, coiled, 3 mm. in length. The mucosa of the dilated lumen distal to the obstruction was thin and smooth, and the lumen was filled with soft, brownish white material. The seed was identified as a piñon nut.

Microscopically, the mucosa and muscularis were relatively normal in the proximal part of the appendix, but in the dilated part the mucosa was flattened. Throughout the slightly edematous lymphoid tissue there were hyperplastic foci. Polymorphonuclear neutrophils were scattered in the muscularis of this part, singly

and in small groups. A few groups of fat cells intervened between the muscularis and the mucosa. The serosa was normal. The diagnosis was acute obstructive appendicitis.

One of us (W. F. B.) has previously reported on the findings in a series of appendixes.[2] The findings included foreign bodies other than fecaliths and pinworms in 2 per cent of the specimens. In 4 appendixes blueberry seeds were found, identified by competent authority. Three appendixes had small brown faceted stones in their lumens, and in 1 of the 3 the stones were identical with those removed from the gallbladder at the same operation. One appendix contained a spicule of bone which was piercing the wall and around which there was an inflammatory reaction, with pus in the lumen. Another appendical lumen contained a piece of keratinized material identified as finger nail. The final case was one in which a toothbrush bristle protruded from the side of a fecalith against the appendical wall. Royster [3] in his monograph stated that bristles, pins, hair, bone, seeds, shot, finger nails, teeth, screws, chewing gum, apple core and nut shells had been found in the appendical lumen. Some authors, of whom Burgess [4] is one, have simply stated that "many fruit seeds" were encountered in their series, but others, e. g., Matterstock [5] and Fitz,[6] place the incidence of foreign bodies in appendical lumens at 12 per cent. So far as is known, the case reported here is the only one in which a foreign body actually was growing in the appendical lumen.

The relationship of acute appendicitis to the lymphoid tissue swelling incident to typhoid inoculation has been made the subject of a separate paper in which 7 other cases are presented. In brief, it can be said that appendicitis in the vast majority of cases [2] is a phenomenon resulting from obstruction to the appendical lumen and that in the case reported here a seed partially occluded the lumen. Only the small amount of lymphoid swelling caused by the reaction to typhoid inoculation was needed to make the occlusion complete and then the chain of events incident to closed loop obstruction was in full swing. Similar lymphoid swelling has been reported to cause appendicitis in such diseases as measles,[7] mumps,[8] scarlet fever [2] and tonsillitis.[9]

SUMMARY

A case is presented in which acute suppurative appendicitis developed after typhoid inoculation because the appendical lumen was obstructed by a sprouting seed.

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Forensic Medicine

CHANGES IN THE MAGNESIUM AND CHLORIDE CONTENTS OF BLOOD FROM DROWNING IN FRESH AND IN SEA WATER

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The pathologic changes disclosed at autopsies on bodies recovered from water are frequently inconclusive in establishing the cause of death. In such instances the opinion that death has been caused by drowning is likely to be based in part on the fact that the body was found in water and in part on the fact that the postmortem examination failed to disclose any other cause of death. Obviously it would be desirable if the diagnosis of death by drowning could be supported by positive rather than negative evidence.

Gettler [1] called attention to the fact that diffusion between intra-alveolar water and capillary blood occurs after death by drowning and observed that the resulting changes in the blood are likely to be more pronounced in the left than in the right side of the heart. Thus after death by drowning in sea water the plasma chlorides may be disproportionately high in the left side of the heart, whereas after drowning in fresh water they are likely to be disproportionately low.

The inconstancy with which such changes are encountered after deaths known to have resulted from drowning, together with the fact that inequalities in the chloride content of samples of blood from the right and the left side of the heart are sometimes found in cases of death known to be due to causes other than drowning, led the authors to investigate certain aspects of the problem of agonal and postmortem migration of electrolytes under controlled experimental conditions.

EXPERIMENTS

All experiments were made on dogs, which were first anesthetized by intravenous injection of soluble pentobarbital. In most instances the amount of soluble pentobarbital given was adequate to quiet the animal but not enough to abolish the palpebral reflexes.

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Chloride was determined by the method of Schales and Schales[2] which consists in titration of a protein-free blood filtrate by a standard solution of mercuric sulfate, diphenylcarbasone being used as the indicator. With this method in this laboratory, added chloride has been recovered with an accuracy of 1 per cent. For the determination of magnesium a modification of the method of Fiske and Logan[3] was used: Following preliminary removal of calcium as calcium oxalate, the blood proteins are precipitated with trichloroacetic acid. The filtrate is concentrated and the magnesium precipitated as magnesium ammonium phosphate. With this method added magnesium has been recovered with an accuracy of 5 per cent.

Antemortem samples of blood were obtained by puncturing the heart through the intact thoracic wall. Postmortem samples[4] were taken from the right and left auricles after opening the chest. The openings in the thorax were made as small as possible and were kept closed during the intervals between sampling to prevent drying of the heart and lungs. In taking the postmortem samples the needle was introduced into the tip of each auricular appendage, and after each sampling the appendages were ligated proximal to the needle holes to prevent loss of serum.

Postmortem changes in the concentration of chlorides and magnesium in the blood were studied in four groups of dogs. The animals of the first group were put to death by clamping the trachea, and some of them were then allowed to remain in room atmosphere for as long as seventy-two hours. Those of the second group were put to death in the same manner but were then kept submerged in either fresh or sea water. The animals of the third group were drowned in a tank of fresh water, and the animals of the fourth group were drowned in sea water. After the animals of groups 3 and 4 were drowned, they were removed from the water and their tracheas were ligated to prevent escape of the inhaled water. They were kept at room temperature (about 75 F.) throughout the period of postmortem observation. Analysis of the sea water used in the experiments disclosed that it contained 1.75 per cent chlorides and 0.115 per cent magnesium. Analysis of the fresh water disclosed that it contained 3.2 parts per million chlorides and 1 part per million magnesium.

Experiment 1.—Six dogs were put to death by mechanical asphyxia (clamping of the trachea). Chloride determinations were made on 5 animals, and magnesium determinations were made on 4. Blood was taken at intervals from the right and left sides of the heart throughout the postmortem period. As indicated in tables 1 and 2, not all of the animals were kept at the same environmental temperature. Dog 1 was kept in a room maintained between 37 and 40 F.; dog 2, in a room maintained between 60 and 70 F., and dogs 3, 4, 5 and 6 in a room maintained between 75 and 85 F.

It may be seen in table 1 that the plasma chlorides in the heart's blood of these animals began to fall between six and twelve hours after death and continued to fall through a postmortem observation period of seventy-two hours. The rate of the loss of chlorides varied to some extent, and it seems likely that the rapidity with which

2. Schales, O., and Schales, S. S.: J. Biol. Chem. **140**:879, 1941.

3. Folin, O.: Laboratory Manual of Biological Chemistry, ed. 5, New York, D. Appleton-Century Company, Inc., 1934, p. 231.

4. It is obviously desirable to obtain comparable specimens from the two sides of the heart. Because of the artefact introduced by sedimentation and clotting, samples of plasma are likely to be more uniform than samples of whole blood.

the chlorides left the plasma increased with the rate at which postmortem autolytic and putrefactive changes developed.

In an animal kept in a cold room (37 to 40 F.) the chlorides in the right and left cardiac chambers were diminished by 25 and 15 per cent below the antemortem level, respectively, at the end of twenty-four hours. At the end of seventy-two hours the plasma chlorides in both sides of the heart had been reduced 27 per cent, or from 375 to 272 mg. per hundred cubic centimeters.

In the animals kept at higher postmortem temperatures the least reduction at the end of twenty-four hours was 27 per cent, or from 406 to 298 mg. per hundred cubic centimeters. The greatest was 45 per cent, or from 467 to 256 mg. per hundred cubic centimeters. At the end of forty-eight hours the percentile reductions in the plasma chlorides of these animals varied between 38 and 48, and at the end of seventy-two hours, between 48 and 51.

The fall in chlorides did not always occur at the same rate in both sides of the heart. In some it occurred more rapidly in the right side and in others more rapidly in the left. The greatest difference between samples from the right and left sides of the heart was observed in the case of dog 5 twelve hours after death and was 40 mg. per hundred cubic centimeters of plasma. Putrefaction had already begun, and both samples showed advanced hemolysis. It should be noted, however, that a difference of 35 mg. per hundred cubic centimeters of plasma was observed between the samples taken from the right and left sides of the heart of dog 1 twenty-four hours after death. In this animal there was neither evidence of putrefaction nor a significant amount of hemolysis to account for the discrepancy.

It appears from the data shown in table 1 that a reduction in plasma chloride of as much as 103 mg. per hundred cubic centimeters, or 27 per cent, below the antemortem level in a nonputrid animal and of 240 mg. per hundred cubic centimeters, or 51 per cent, below the antemortem level in a putrid animal may represent normal postmortem changes. It also appears that differences as great as 40 mg. of chloride per hundred cubic centimeters may be encountered in postmortem samples of plasma simultaneously obtained from the two sides of a dog's heart.

In table 2 it is shown that the concentration of magnesium in the plasma increased after death. In 2 animals from which samples were taken relatively soon after death the elevation was apparent within six hours.

In an animal kept in a cold room (37 to 40 F.) the plasma magnesium in the right and left chambers was increased by 38 per cent above the antemortem level, or from 2.3 to 3.7 mg. per hundred cubic centimeters by the end of the first twenty-four hours. At the end of seventy-two hours the increase was by 157 and 191 per cent, or to 5.9 and 6.7 mg. per hundred cubic centimeters, respectively, in the right and left chambers.

In 4 animals kept at higher postmortem temperatures the plasma magnesium of the cardiac blood was more than doubled at the end of twenty-four hours. At the end of forty-eight hours it was increased to between three and six times its antemortem level. In dog 3 the plasma magnesium reached 20.8 mg. per hundred cubic centimeters, compared with an antemortem level of 2.4 mg.

As was observed in the case of chlorides, the magnesium levels did not always change at the same rate in the two sides of the heart. In some instances that in the right rose more rapidly, and in others, that in the left. The greatest difference observed at any time in 11 pairs of postmortem samples was 0.9 mg. per hundred cubic centimeters.

It appears from the data shown in table 2 that an increase in the plasma magnesium of as much as 4.4 mg. per hundred cubic centimeters in a nonputrid

TABLE 1.—*Postmortem Changes in the Concentration of Plasma Chloride in the Right and Left Sides of the Hearts of Dogs Killed by Tracheal Compression*

Time	Dog 1 Postmortem Room Temperature 37 to 40 F.			Dog 2 Postmortem Room Temperature 60 to 70 F.			Dog 3 Postmortem Room Temperature 75 to 85 F.			Dog 4 Postmortem Room Temperature 75 to 85 F.			Dog 5 Postmortem Room Temperature 75 to 85 F.		
	Side of Heart			Side of Heart			Side of Heart			Side of Heart			Side of Heart		
	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.
Ante mortem	375	375	..	467	467	..	406	406	..	410	410	..	413	413	..
Post mortem															
15 minutes	...	...	..	...	...	..	...	...	..	416	429	13	416	429	13
6 hours	...	...	..	...	...	..	406	410	4	403	422	19	...	...	..
12 hours	...	...	..	...	...	..	381	...	..	...	...	..	314	354	40
24 hours	282	317	35	256	278	22	298	302	4	276	276	0	276	305	29
48 hours	...	...	..	253	243	10	231	...	..	262	256	6	...	...	..
72 hours	272	272	0	232	227	5	212	...	..	...	...	..	...	...	..

TABLE 2.—*Postmortem Changes in the Concentration of Plasma Magnesium in the Right and Left Sides of the Hearts of Dogs Killed by Tracheal Compression*

Time	Dog 1 Postmortem Room Temperature 37 to 40 F.			Dog 2 Postmortem Room Temperature 60 to 70 F.			Dog 3 Postmortem Room Temperature 75 to 85 F.			Dog 6 Postmortem Room Temperature 75 to 85 F.		
	Side of Heart			Side of Heart			Side of Heart			Side of Heart		
	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.
Ante mortem	2.3	2.3	...	2.3	2.3	...	2.4	2.4	...	2.4	2.4	...
Post mortem												
15 minutes	...	...	...	...	...	...	2.6	2.3	0.3	2.3	2.6	0.3
6 hours	...	...	...	...	...	...	3.4	3.3	0.1	3.3	3.4	0.1
12 hours	...	...	...	...	...	...	5.8	5.2	0.6	5.6	5.8	0.2
24 hours	3.7	3.7	0.0	6.8	5.9	0.9	7.3	...	...	7.3	...	...
48 hours	...	...	...	8.6	8.5	0.1	16.0	...	...	16.0	...	...
72 hours	5.9	6.7	0.8	10.4	10.2	0.2	20.8	...	...	...	...	...

animal and one of as much as 18.4 mg. per hundred cubic centimeters in a putrid animal may result from postmortem change. It also appears that a difference as great as 0.9 mg. of magnesium per hundred cubic centimeters of plasma may be encountered in postmortem samples simultaneously obtained from the two sides of a dog's heart.

EXPERIMENT 2.—This experiment was undertaken to learn whether or not postmortem submersion of an animal already dead of causes other than drowning will modify the rate and the character of the chemical changes that normally take place in the plasma after death.

Two lightly anesthetized dogs were killed by compression of the trachea. One (dog 7) was then submerged for seventy-two hours in fresh water, and the other (dog 8) was submerged for forty-eight hours in sea water.

The antemortem plasma chloride content of a sample taken from the heart of dog 7 was 432 mg. per hundred cubic centimeters. After seventy-two hours' submersion in fresh water the plasma chloride levels in the right and left sides of the heart had dropped to 266 and 278, respectively. The plasma magnesium concentration of an antemortem sample taken from this dog was 1.9 mg. per hundred cubic centimeters. After submersion of the dog in fresh water for seventy-two hours the plasma magnesium had risen to 8.0 mg. per hundred cubic centimeters in the right side of the heart and to 7.7 mg. per hundred cubic centimeters in the left.

The antemortem value of the plasma chloride of a sample taken from the heart of dog 8 was 448 mg. per hundred cubic centimeters. After forty-eight hours' submersion in sea water the plasma chloride levels in the right and left sides of the heart had dropped to 368 and 328 mg., respectively. The concentration of plasma magnesium in an antemortem sample taken from this dog was 2.1 mg. per hundred cubic centimeters. After forty-eight hours' submersion in sea water the concentration in the right side of the heart had increased to 6.6 mg. per hundred cubic centimeters and that in the left to 6.3 mg. per hundred cubic centimeters.

Although both the fresh and the sea water tanks remained at approximately the same temperature (60 to 70 F.), there was considerable difference in the rate at which putrefaction developed in the submerged animals. There was little evidence of putrefactive change in dog 8 after forty-eight hours' submersion in sea water, whereas putrefactive changes were well developed in dog 7 at the end of seventy-two hours. It seems likely that the relatively small loss of chlorides from the heart's blood in dog 8 (82 mg. from the right and 122 mg. from the left) as compared with control dog 2 (see table 1), which was kept in the air at approximately the same temperature, could be better accounted for by the fact that the latter putrefied more rapidly than the former than by the assumption that sea water had entered the lungs of dog 8 after death. There was neither chemical nor pathologic evidence that water had entered the lungs of either of the animals that were submerged after death.

EXPERIMENT 3.—Two dogs were drowned by submersion in a tank of fresh water. The first (dog 9) was lightly anesthetized and struggled for about a minute immediately after submersion, during which time the animal held its breath. Immediately thereafter it lapped water vigorously for a minute or two and then vomited. The dog then began to inhale water, at first slowly and later rapidly. Toward the end the respiratory movements became irregular and spasmodic. All respiratory activity ceased at the end of about four minutes, and the heart continued to beat for several minutes thereafter. The second animal (dog 10) was more deeply anesthetized and did not struggle after being placed in the tank. It did not lap water, and all respiratory movement stopped after about two minutes' submersion. The heart beat was not perceptible after the cessation of respiratory movement.

Each dog after respiration had ceased was placed on the operating table and kept at room temperature (about 75 F.) throughout the duration of the experiment. The plasma chloride determinations for the two animals are shown in table 3.

Within fifteen minutes after death the plasma chloride concentrations in the right and left sides of the heart of dog 9 were reduced by 41 and 70 per cent, respectively. The difference between the chloride concentrations in the two sides of the heart at this time was 134 mg. The chloride concentration in the right side of the heart continued to fall whereas that in the left side remained relatively stationary. At the end of seventy-two hours the chloride had dropped 62 per cent below the antemortem level in the right side of the heart and 69 per cent in the left. During the first twenty-four hours after death the difference between the chloride concentrations in the right and left sides of the heart was in excess of 75 mg. per hundred cubic centimeters, which was greater than had been observed in any of the animals in the control series. After putrefaction was established (forty-eight hours post mortem) the differences in chloride concentration were diminished to a point at which they were no greater than some of the differences that were observed in control animals.

TABLE 3.—*Changes in the Concentration of Plasma Chlorides in the Right and Left Sides of the Hearts of Two Dogs Drowned in Fresh Water*

	Dog 9			Dog 10		
	Side of Heart			Side of Heart		
Time	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.
Ante mortem	454	454	0	397	397	0
Post mortem						
15 minutes	269	135	134	342	352	10
6 hours	...	...	...	294	307	13
12 hours	256	144	106	...	...	..
24 hours	227	150	77	269	243	26
48 hours	...	...	..	...	...	..
72 hours	173	141	32	...	...	..

Dog 10, which was more deeply anesthetized than dog 9, died without a struggle and soon after being submerged. This may account for the fact that there was less evidence of plasma dilution. Within fifteen minutes after death the chlorides in the right side of the heart had dropped 55 mg. and those in the left side 45 mg. In contrast it should be noted that in the control animals (see table 1) there was no significant change in the chloride concentrations of samples taken fifteen minutes after death. At the end of six hours the plasma chlorides of dog 10 were reduced by 26 per cent in the right side of the heart and by 23 per cent in the left side. No such dilution had been observed in control animals within the first six hours after death. At no time in dog 10 were the differences observed between the concentrations of chlorides in the right and left sides of the heart greater than some of those that were observed in control animals.

In both of the animals drowned in fresh water the postmortem reduction in plasma chloride concentrations occurred earlier than it did in the animals of the control series. In one of the drowned animals the difference between the chloride concentrations in the right and left chambers caused by disproportionate dilution of the blood in the left side was significantly greater during the first twenty-four hours after death than that in the control animals. In both drowned animals there was marked hemolysis of the blood in the left auricle as early as fifteen minutes after death, whereas in the control series a significant degree of hemolysis (5 per cent hemoglobin in the plasma) did not develop until six hours or more after death.

EXPERIMENT 4.—Three dogs were anesthetized lightly and were then drowned by submersion in sea water. In each the reaction to submersion was similar to that observed in dog 9. After all respiratory movements had ceased, the animals were removed from the water and samples of blood for chloride and magnesium analysis were taken from the right and left sides of the hearts at the intervals indicated in tables 4 and 5.

It may be seen that during the first twenty-four hours after death the differences between both the chloride and the magnesium concentrations in the two sides of the heart were greater than had been observed at any time in animals of the control

TABLE 4.—*Changes in the Concentration of Plasma Chlorides in the Right and Left Sides of the Hearts of Dogs Drowned in Sea Water*

	Dog 11			Dog 12			Dog 13		
	Side of Heart			Side of Heart			Side of Heart		
Time	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.
Ante mortem.....	438	438	..	435	435	..	442	442	..
Post mortem									
15 minutes.....	483	537	54	...	...	..	...	...	..
6 hours.....	403	570	167	...	...	..	...	...	..
12 hours.....	397	601	204	493	541	48	467	547	80
24 hours.....	...	...	...	390	480	90	339	438	99
48 hours.....	336	342	6	381	422	41	330	368	38
72 hours.....	...	...	...	384	406	22	323	342	19

TABLE 5.—*Changes in the Concentration of Plasma Magnesium in the Right and Left Sides of the Hearts of Dogs Drowned in Sea Water*

	Dog 11			Dog 12			Dog 13		
	Side of Heart			Side of Heart			Side of Heart		
Time	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.	Right, Mg. per 100 Cc.	Left, Mg. per 100 Cc.	Difference, Mg.
Ante mortem.....	2.5	2.5	....	2.5	2.5	....	1.9	1.9	....
Post mortem									
15 minutes.....	5.2	15.3	10.1	....	....	....	....	....	....
6 hours.....	...	25.0	....	....	....	....	....	....	....
12 hours.....	10.6	29.5	18.9	9.7	22.7	13.0	9.1	19.3	10.2
24 hours.....	....	....	....	10.6	19.4	8.8	12.4	18.0	5.6
48 hours.....	13.0	20.6	7.6	14.7	16.5	1.8	14.7	15.0	0.3
72 hours.....	....	....	....	20.4	19.6	0.8	22.5	22.0	0.5

series. The least difference between chloride concentrations in the right and left chambers within the first twenty-four hours after death was 48 mg. and the greatest 204 mg. The least difference between magnesium concentrations was 5.6 mg. and the greatest 18.9 mg. In all observations made within twenty-four hours after death the concentrations of chlorides and magnesium in the left were significantly greater than those in the right side of the heart. After twenty-four hours the differences in both the chloride and the magnesium concentrations between the two sides of the heart became less pronounced.

Even after putrefaction was fully developed in the animals drowned in salt water the plasma chlorides did not fall below 300 mg. per hundred cubic centimeters, whereas the chloride levels in putrefied animals of the control series were ordinarily much lower. Analysis of the gastric contents of animals drowned in sea water disclosed magnesium concentrations that varied between 0.075 and 0.100 per cent.

COMMENT

It has been observed in dogs that striking changes take place in the chloride and the magnesium content of the heart's blood after death. A decrease in chlorides and an increase in magnesium are apparent within six to twelve hours post mortem and become progressively greater during the next two or three days. By the end of seventy-two hours the chlorides may diminish by as much as 50 per cent and the magnesium may increase by eightfold or more. Although the rate at which these changes occur is affected by the environmental temperature, they are not completely inhibited by room temperatures as low as 40 F. The results obtained from analysis of human blood samples indicate that similar postmortem changes may occur in man.

It was observed that the postmortem chemical changes do not always progress at the same rate in the two sides of the heart. In some animals they occur more rapidly in the right side and in others in the left.

The differences between the concentrations of plasma chloride in the right and left sides of the heart as determined on 16 pairs of postmortem samples from control animals (experiments 1 and 2) ranged between zero and 40 mg. per hundred cubic centimeters. The distribution of the differences followed a normal curve, and statistical analysis disclosed the standard deviation of the differences to be 20.6. It would appear that a difference in excess of 60 mg. (approximately three times the standard deviation of the differences observed in control animals) would constitute evidence that some unusuaal unilateral alteration in electrolyte concentration had taken place.

The differences between the concentrations of plasma magnesium in the right and left sides of the heart as determined on 13 pairs of postmortem samples from control animals varied between zero and 0.9 mg. per hundred cubic centimeters. These differences also appeared to follow a normal distribution curve, and their standard deviation was 0.42. As with the differences in chloride concentration it is felt that a difference in the concentrations of plasma magnesium in the two sides of the heart in excess of three times the standard deviation (about 1.25 mg. per hundred cubic centimeters) should be regarded as evidence of abnormal unilateral concentration or dilution.

In observations on human material chloride differences as great as 50 mg. and magnesium differences as great as 1.0 mg. per hundred cubic centimeter of plasma were encountered in postmortem samples taken from the right and left sides of the heart of persons dead of causes other than drowning.

Within fifteen minutes after drowning in fresh water the concentrations of plasma chlorides in both sides of the hearts of the two animals used in experiment 3 were found to be reduced to levels not ordinarily encountered in any of the control animals until much later in the post-

mortem period. The generalized dilution of blood of these animals was interpreted as evidence that considerable antemortem diffusion of electrolytes had occurred between the pulmonary capillaries and the fluid that had been aspirated into the lungs. Similar generalized changes in the electrolyte concentration of the blood have been observed in human subjects after death by drowning.

In one of the 2 animals that had been drowned in fresh water the chlorides in the left side of the heart during the first twenty-four hours after death were found to be much lower than those in the right. The difference between the chlorides in the two sides of the heart of this animal was significantly greater than the greatest difference observed in the control series and indicates that disproportionate dilution of the blood in the left side of the heart had occurred. It was observed, however, that the difference became less as the hours passed and after the development of putrefaction became so small as to lack significance.

In the other animal drowned in fresh water disproportionate dilution of electrolytes in the left side of the heart was not observed even in the samples which were taken early in the postmortem period. It is perhaps significant that this animal was more deeply anesthetized than any of the other animals and died with relatively little struggle and within two minutes after submersion. Although the reason why disproportionate dilution of the blood in the left side of the heart occurred in one animal and not in the other is obscure, it seems likely that the manner in which the terminal heart failure occurred may have been an important factor. If the agonal circulatory collapse is gradual rather than abrupt, it is entirely possible that even though the terminal ventricular contractions propel a certain amount of chemically altered blood out of the pulmonary vessels into and through the left side of the heart, so much of it is pooled in the dilated vessels of the systemic circulation that significant terminal chemical differences of blood are established between the right and left sides of the heart. If, however, the agonal circulatory collapse is sudden, so that blood is circulating actively through both the pulmonary and the systemic circuits until the moment of asystole, the chemical differences of the blood contained in the two sides of the heart might well be so slight as to be imperceptible. If the foregoing hypothesis is correct in the case of the dog, it may also serve to explain the absence of disproportionate electrolyte concentration that is sometimes encountered in persons who have died by drowning.

A striking change observed in both the animals that were drowned in fresh water was early hemolysis of the blood, particularly of that in the left side of the heart. Samples of plasma withdrawn as early as fifteen minutes after death contained in excess of 5 per cent hemoglobin, whereas in the control animals a comparable degree of hemolysis was not observed until many hours had elapsed.

Immediately after death from drowning in salt water it was observed that the chlorides and the magnesium were elevated in both sides of the heart. Chloride levels observed during the first six hours after drowing in salt water were higher than the levels observed at any time in the control animals. Magnesium levels during the first twelve hours after drowning in sea water were consistently higher than those observed in control animals prior to the development of putrefaction. The increase in chlorides and magnesium was greater in the left than in the right side of the heart in all 3 animals drowned in sea water. Even after the development of putrefaction the plasma chlorides of these animals failed to fall below 300 mg. per hundred cubic centimeters, whereas in the control series chloride levels of 300 mg. were invariably present after putrefaction had developed.

Additional observations on animals dead of drowning in sea water included that of a relatively high (0.075 to 0.100 per cent) concentration of magnesium in the gastric contents and that of delay in postmortem hemolysis of the heart's blood.

There was neither pathologic nor chemical evidence that significant concentration or dilution of the heart's blood occurs when an animal dead of causes other than drowning is submerged in salt or fresh water.

SUMMARY

In both dogs and man a progressive loss of plasma chlorides accompanied by an increase in plasma magnesium represents a normal postmortem phenomenon.

These changes do not always occur at the same rate in the two sides of the heart. In dogs differences in chlorides as great as 40 mg. and in magnesium as great as 0.9 mg. per hundred cubic centimeters of plasma may be encountered within twenty-four hours after death. Comparable differences have been observed in man.

After drowning in fresh water not only may the plasma chlorides be reduced in both sides of the heart to levels not ordinarily encountered in comparable samples from control subjects but the reduction may be significantly greater in the left than in the right side.

After drowning in sea water the chlorides and the magnesium are increased in both sides of the heart to levels not ordinarily encountered in control subjects and the increases are likely to be significantly greater in the left than in the right side.

The agonal and early postmortem differences between the chemical constitution of the blood on the left and that of the blood on the right side of the heart which may exist after drowning in either fresh or sea water tend to disappear as putrefaction progresses.

General Reviews

LEPROSY FROM THE HISTOLOGIC POINT OF VIEW

"quod ante haec dua annorum milia vitae origines in ipsis fortibus corrupuit" . . . —Ihm.

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Danielssen and Boeck, in 1847, illustrated histologic studies of leprosy for the first time. They described oblong cells comprising the nodules, larger than the usual inflammatory cells. Simon, in 1848, illustrated a section through a nodule, describing its cellular and connective tissue structure. Although Danielssen and Boeck described yellowish brown granules in the lesions, they inclined toward the idea of leprosy as a hereditary rather than as an infectious disease. There are a few other descriptions in the 1850's and early 1860's, such as that of Kobner, who spoke of the infiltrations as small in the deeper layers of the skin, enlarging near the surface and becoming continuous in the papillary layer, ". . . distributed about vessels as well as sebaceous or sweat glands."

Among the numerous descriptions of leprous lesions that followed during the period preceding 1879 (when Neisser demonstrated the acid-fastness of Hansen's bacillus), that of Virchow is one of the more intelligible:

> . . . In connection with the cells, I note that at the height of their development they consist of round, pale, finely acinous, easily perishable elements with at most a moderately large and at the same time granular nucleus with nucleoli. In the fresh state there is a particularly notable peculiarity, namely, their marked tendency to form a sort of vacuole, apparently from taking up water, so that they acquire under the circumstances a wholly physaliferous[1] appearance.

Virchow noted many features of the nodule—the flattened epidermis, the loss of hairs, the involvement of arrectores pilorum muscles, the accumulation of fat as the lesions aged and the development of new processes above the old. He derived the lepra cells from connective tissue cells, in which he found nuclear divisions and described fibrous nerves.

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1. From φυσαλλις, a little bladder, hence a bubble, so that the word means foamy.

Gerhard Armauer Hansen published his conviction of the etiologic importance of the "brown granules" in 1874. He adopted the expression from Danielssen and had used it previously to this time but not with such certainty. That Hansen recognized the individual bacilli forming the masses as the essential units is clear from his descriptions:

> . . . The cells, but not the brown elements, swell considerably in water, and if one examines them under a strong lens, one discovers in many of them, besides granules, also rod-shaped bodies. At times one will find the rods together in bunches crossing each other at very sharp angles.

Neisser's demonstration brought the incunabular period of the concept of leprosy to a close. It was followed by a paper by Hansen, giving many details of the relation of the bacilli to cells and tissues, and by another more extensive descriptive article by Neisser, in which he stated that Hansen had rushed into print to enjoy precedence to which he was not entitled. During the last two decades of the nineteenth century a large number of articles appeared on the anatomy and the histology of leprosy, with some description of every bare anatomic detail. Hansen in 1901 exclaimed that the literature of leprosy was "already vast enough," but with the exception of the period of the war it has increased steadily and voluminously.

TERMINOLOGY

Danielssen and Boeck divided leprosy into two forms, the tubercular and the neural. A considerable evolution in terms has taken place in ninety-five years. Although "tubercular" is still used at times, it has given way in many instances to "cutaneous," "granulomatous," "nodular" and "lepromatous"; the last is much in use today. Tubercular leprosy is not to be confused with tuberculoid leprosy (described in later paragraphs). At the other extreme, the term "neural leprosy" has had a stormy career. The discovery has been made repeatedly that the milder forms of leprosy are ipso facto those with few bacilli. The term "leprid" has been much used to signify a macule without bacilli or with extremely few organisms, and "neuroleprid" to imply a relation to cases in which nerve changes are outstanding. The broad, flat lesions led Hansen and Looft to the term "maculoanesthetic leprosy" as a partial substitute for "neural leprosy," and the expression "mixed leprosy" is an acknowledgment that many cases present macules, anesthetic areas, nodules and other changes.

PRIMARY AND TRANSITIONAL STAGES

Probably the first important studies of leprosy in its early stages were those begun by Gomez, Avellana Basa and Nicolas in the Philippine Islands. They followed the children born to institutionalized lepers to discover early lesions. These have been supplemented by additional studies by Lara and de Vera, Rodriguez (1926, 1932), Chiyuto, and

Nolasco and Lara. Other, not wholly comparable studies of children have been instituted by Cochrane and Rajogaplan in India, Wayson in Hawaii, de Souza Araujo in Columbia and Rodrigues in Brazil.

The respiratory and gastrointestinal tracts have been considered by Lowe and Muir to be possibly of no importance compared with the skin as a portal of entry of the bacillus, and the question of a primary lesion of the skin akin to the Ghon tubercle or the chancre of syphilis has often been raised. An interesting commentary on this was offered by Nolasco and Lara in their recent description of a case of infantile leprosy, with a review of other published cases thereof. The upper air passages, which are so regularly the seats of leprous infection, offer an easy and simple explanation, which proves on the whole unsatisfactory (Solis and Wade). Nolasco and Lara suggested that previous lesions of the skin, often due to scabies, offer a site for the development of first lesions, possibly affording a portal of entry for the organisms. Of more direct interest is their finding that in 11 of 14 cases of genuinely early involvement the disease was tuberculoid in histologic character, i. e., showing principally tubercle formations of epithelioid and giant cells.

The first case of tuberculoid leprosy described was that of Montgomery, who saw in a lesion of the face giant cells which were "too circular" and "surrounded by one row, usually complete, of round nuclei." He interpreted these as hyalin-filled capillaries cut in cross section, the nuclei representing hyperplastic endothelium. Nonetheless, he made a remarkably apocryphal statement concerning sections that were examined fruitlessly for bacilli: "This is exactly what was to have been expected." Jadassohn presented a clearcut case of tuberculoid leprosy, and Arning described a nerve abscess with tuberculoid and caseous changes. Jadassohn's case showed epithelioid cell tubercles and some caseation. Blaschko and Glück told of having seen somewhat similar changes. Additional examples followed through the years, from Hodara, Tshlenow, Brutzer, Klingmüller (1900), Tiéche, Merian, Kedrowsky, E. Hoffmann, Unna Jr., Bruusgaard, Darier, Pautrier and Boez, Tebbut and Molesworth, Balina and Basombrio, and Tisseuil. But the modern trend began with the publication by Wade and Pineda of the results of their survey of "negative lepers" at Culion, Philippine Islands, among whom they found an astonishingly large number showing this type of process.

Wade distinguished two forms of tuberculoid leprosy, major and minor. Marked clinical differences, with the usual presence of bacilli in the major and their absence from the minor form, serve to distinguish them. Concerning lesions of the major form, Wade and Rodriguez (1939) wrote:

> . . . On the whole they differ rather widely from the ordinary chronic tuberculoid leprids, in which the granulomatous foci are more or less distinct. . . . For

the most part the granuloma is more diffuse and less differentiated, the component cells not distinctly of the epitheloid form or if so not aggregated in characteristic foci; giant cells are not numerous or conspicuous or typical.

Although Wade saw such lesions regress completely in 1 case, he and Rodriguez (1940), des Essarts and Lefrou (1936) and Schujman described the transition of this form into the frankly nodular variety. I have seen a few cases in which the changes were mixtures of tuberculoid and lepromatous reactions and a case in which the cells were curiously neither epithelioid nor vacuolated but hybrids with many bacilli. It seems clear that transitions between major tuberculoid and nodular leprosy must not be altogether rare.

Most of the writings, old and new, are of the minor tuberculoid lesions, which are meant by the unspecified use of the word. Brutzer described the cells forming tubercles particularly about capillaries, but it has since been recognized that they occur also in much the same positions as the bacillus-containing foci of macular or nodular lesions, closely related to the appendages of the skin.

The foci occur often in a layer close to the surface, perhaps, as Klingmüller (1927) said, because "the papillary area in leprosy as in tuberculosis provides a site for the removal of bacilli from the blood stream." Wade noticed that the cells of the tubercles commonly lie in actual contact with the cells of the basal layer of the epidermis, with fraying of the cytoplasm of the latter. A long series of incompletely separate foci may extend along the surface, flattening the epidermis only over small areas, thus giving rise to the clinical appearance of groups of minute papules.

The actual arrangements and developments of the epithelioid cells, giant cells and lymphocytes which form the bulk of the foci are quite variable and probably dependent on the status of the disease as a whole. The giant cells may be as large as those in tuberculosis but rarely show the crescentic arrangement of polarized nuclei. More often they are round, with sharply limited cytoplasm, which in the center shows fine granules against a nearly clear background. The nuclei lie at the periphery, sometimes with spherical regularity. Variations in size and shape are countless; the giant cells may resemble foreign body giant cells, and occasionally contain foreign bodies. Des Essarts and Lefrou (1934) distinguished the character of the tubercles of leprosy from those of tuberculosis histologically as showing much more uniform tinctorial properties but much more irregularity otherwise. The leprous ones affect the epidermis less, are more vascular and contain a greater variety of cells. Old leprous tubercles are commonly sharply outlined histologically by a thin fibrous capsule, but in earlier lesions the peripheral lymphocytes and histiocytes mingle loosely with the neighboring collagen fibers.

In sections the tuberculoid foci may appear discrete, but whether in serial sections they would is doubtful, as foci often originate in accumulations of lymphocytes and other cells along blood vessels and nerves, and many of the lesser lesions appear as minute groups of epithelioid cells without giant cells in perivascular cuffs of ordinary chronic inflammatory cells. With regression of the lesions, atrophic changes take place in the tubercles to the point of complete disappearance. An extensive lesion may leave as a residue only the collapsed framework of the granuloma.

Tisseuil (1930) suggested that the tuberculoid foci of epithelioid cells (without giant cells) represent intermediate stages of development, and Rabello Jr. issued (1937) another more elaborate classification of tuberculoid lesions into (1) pretuberculoid, (2) sarcoid, (3) lupoid or follicular, with bacilli present, and (4) colliquative with caseation. Portugal adopted this classification, in which the sarcoid would correspond to Wade's minor tuberculoid, the lupoid to the major and the colliquative to the nerve abscess or bullous ulcerative (lazarine) lesion.

Caseation, necrosis or signs of simple inflammation are usually absent from the lesions of tuberculoid leprosy. There is another variety, however, which appears rarely, in which widespread ulceration of the skin over the lesions follows the formation of bullae. Cases of this type, as described by Nicolas, Gaté and Ravault, Ryrie, Lowe and Chatterji, Rodriguez (1935) and Wade and Rodriguez (1940), for which the term "lazarine leprosy" has been used, seem to be cases of Wade's major tuberculoid variety.

The rarity of bacilli in the lesions of minor tuberculoid leprosy is a consistent feature. When bacilli are found, they are in relation to the epithelioid cell foci, rarely in giant cells, most often within outer marginal epithelioid cells or in undifferentiated wandering cells at the margins of epithelioid cell foci, singly rather than in groups. However, if a group of bacilli is formed, the cell becomes vacuolated and identical with the lepra cell. The epithelioid cells may contain a diffuse fine deposit of lipoid. Among different examples of tuberculoid lesions it is probable that some can be found showing all stages of development from minor to major forms, as well as regressive lesions in which no bacilli can be found in spite of exhaustive search, for which Merian recommended the use of antiformin (a strongly alkaline solution of sodium hypochlorite) and in the study of which fluorescent microscopy might prove to have some value.

Wade and also Lowe inclined to the belief that all macular leprosy is basically tuberculoid. On the other hand, Portugal expressed the opinion that a distinction should be maintained between "simple" and tuberculoid leprids. Ermakova found the lesions in most of his cases

to be simple leprids without tuberculoid changes. Ota and Sato (1937) expressed the opinion that tuberculoid leprosy should not be considered a special form of the disease. Montel and Bablet preferred the term "tuberculids" of leprosy. Rabello Jr. expressed the belief that tuberculoid leprosy represents a transition from the neural to the nodular form in the sense that it is a temporary stage, which shows differences in development from minute groups of epithelioid cells to the fully formed tubercles (Parmakson).

Hughes summed up the general belief that "tuberculoid leprosy is the natural evolution of immunity in the disease" and that it represents the peak of the local response.

There is also the peculiar problem of Boeck's sarcoid and the marked similarity of that lesion histologically to fully developed tuberculoid leprosy without bacilli (Filho; Reenstierna; de Souza and Adjuto). Lisi and Sebastiani used the expression "sarcoids of leprosy," and Mottat emphasized the similarity of tuberculoid lesions to other cutaneous sarcoids. Reenstierna remarked that a diagnosis of Boeck's sarcoid is not likely to be made in communities with a high rate of leprosy and pointed to the lack of consideration of leprosy in cases of this disease in zones where the little leprosy present might be predominantly of the more benign tuberculoid type.

TYPES OF LESIONS

Macules and Leprids.—Although every possible variation in histologic change is seen in leprosy, and although one may subscribe to the dictum of Leloir (1885), "Il n'y a q'une lèpre, a l'évolution variable" (There is only one leprosy variable in its evolution), it is necessary to point to one phenomenon which distinguishes the spreading macule from the nodule. The macule, irrespective of its histologic appearance, is commonly multiple, annular and intermittently active at the borders only. As it advances there is left a central area which is anesthetic and partly depigmented and which shows histologically only banal cellular changes. The central part of the macule is resistant to further macular spread. But this area is as susceptible as any other to the development of a lepromatous lesion. Another ancient truism emphasizes the perplexity: The histologic changes of the young nodule are identical with those of the active nontuberculoid macule. Piscane said that the differentiation of neural from nodular lesions is quantitative, not qualitative; or there is Darier's statement (1897): "Par un série insensible de gradations elles se rapprochent des léprômes en nappe" (By an imperceptible series of gradations they are brought nearer to diffuse lepromas). Klingmüller (1902), studying reports of multiple biopsies in 3 cases of macular leprosy, stressed the numbers of bacilli present as an important factor

in the variability of the picture and observed the spread of macules irrespective of the nodular formations.

The earliest or slightest lesion consists of cells about the vessels of the superficial papillary plexus of the dermal papilla. There are usually other small infiltrations about small vessels in the upper part of the corium with which it is continuous. The nature of the cells becomes disputable as they acquire bacilli, but if no bacilli are present, they are chiefly lymphocytes and wandering cells such as normally constitute the adventitial cells of the capillaries. Thus in its simplest form there is nothing characteristic about the cellular infiltration (Dubois). Rare bacilli are found most often in the phagocytic cells about the papillary plexus (Lie, 1935). In ordinary sections the bacilli lie in the cytoplasm, and Klingmüller illustrated minute vacuolar halos about the single organisms. Lie, searching for rare bacilli, was able to find them in all of 10 cases; he stressed the necessity of searching through many sections, or during brief periods of activity. Klingmüller (1927) attributed an origin from the blood stream to tuberculoid lesions and in 1930 made this statement: "The cutaneous macular eruptions of neural leprosy are to be construed as seedings of bacilli from the blood stream." There is little else in the literature that agrees with this strict interpretation of the origin of macules, while references to a hematogenous origin of nodules are abundant.

The central parts of macules have been frequently examined, and Hansen (1882) observed that in most there appears some atrophy of the epidermis, of its hairs and glandular appendages, while the cellular reaction may amount to almost nothing, perivascular lymphocytes, monocytes, tissue mast cells and others. Small nerves may show myelin wholly or partly absent, endoneurial connective tissue increased and Schwann cells increased, i. e., wallerian degeneration or some fibrosis; or it may be impossible to recognize small nerves as such. Laaft found any remaining bacilli broken up and arrectores pilorum muscles atrophic.

Nodules.—Histologically, the variety of macules ranges from Arning's leprid with its rare bacilli to other lesions whose superficial infiltrating cells, though few, are stuffed with prodigious numbers. Since Philippson (1893) wrote of the vascular lesions of leprosy, there have been innumerable suggestions that the bacilli which lead to the formation of nodules reach the skin by way of the blood stream. In rare cases small nodules are sprinkled over the whole body (Soulage and Nadessin).

Herxheimer and also Riecke described accumulations of bacilli in endothelial cells of small vessels, their illustrations being reproduced in Klingmüller's opus magnum of 1930. I have presented reasons for believing that these are rather common developments in old lesions and that they are not a result of embolism of small vessels as Herxheimer

suggested. Probably the early nodules would be found in relatively normal skin, where bacilli have frequently been described. Klingmüller found them there rather commonly, particularly in advanced leprosy, suggesting that of the many that may be deposited few develop into nodules. The development follows the geographic plan of the skin, as infiltrations along or within its structures, until the enlarging infiltrations destroy the intervening connective tissue and coalesce. Even in the solid lesion the separate lobules remain fairly distinct. The epidermis is thinned and flattened, and beneath it is a thin uninvolved layer of collagen fibers separating it from the leproma proper. This boundary strip consists of the stretched papillary layer of the corium.

The individual areas also enlarge by the addition of granulomatous cells and by the spread of bacilli between the fibers of the corium, where they follow and are closely applied to blood vessels. Bacilli can be found a short distance from the main areas, lying free in tissue spaces, and in acute phases these extracellular bacilli are sufficiently common to permit tracing their connection to the parent foci. That bacilli lie within the lumens of such capillaries as well as in their adventitial cells is doubtful, but the supposition is supported by Klingmüller, while Berengrün, and Muir, maintain that the spread is by way of lymphatic capillaries. Individual lepromatous masses often become sharply outlined, but no capsule develops.

THE LEPRA CELL

The nature of the bacillus-containing cells that form the bulk of the lepromatous lesion has been one of the most discussed topics in leprosy. Herxheimer stated:

> . . . The lepra cells have been variously designated, and we see here a gradual development of beliefs wholly parallel to those with regard to the cells of tuberculosis. Neisser thought of connective tissue cells, but regarded his so-called "globi" as stalactites of lymphocytes. Most French authors considered large mononuclear cells as the basic cells. Then plasma cells were dragged in, as by Gurd, while Unna, who generally denied the existence of "lepra cells," believed that plasma cells surrounded bacillary emboli. Other authors derived the lepra cells from fixed tissue cells. One group thought of them as being principally endothelial cells. Numerous authors found in the skin transitions from *fixed* connective tissue cells to the vacuolated lepra cells, as Virchow indicated.

From the writing that has been done on this subject there issue a few clear points. Opinions are often as much a product of academic tradition as of observation. The nature of the lepra cell is not a question peculiar to leprosy. The cells which differentiate into the vacuolated, bacillus-containing and lipoid-containing Virchow lepra cells occur in any granulomatous lesion. It may be said that leprosy offers one example of how the mononuclear cells of labile capacity are altered under special

conditions. There is little agreement among histologists and pathologists about the origin and interrelation of these cells.

Chuma and Gujo reported the result of injecting lithium carmine and india ink directly into the nodules. It was found that the cells which contained bacilli readily phagocytosed the dye particles. This was confirmed by Koike, and in recent years the treatment of leprosy by intravenous injection of several dyes (Gougerot and Degos) has further shown that leprous lesions with their abundant phagocytic cells take up many more dye particles than the normal skin. The cells, especially the multinuclear cells, may occasionally phagocytose various particles, such as hemosiderin (Ermakova) and elastica bodies (Mitsuda).

The numerous theories of the origin of the bacillus-containing lepra cell have been recited and reviewed by Herxheimer, Klingmüller and many others and need not be repeated at length. It is a problem of general pathology, not of leprosy, of which MacCallum wrote:

> . . . The attempts directed toward subdivision and classification have not been very successful and efforts to trace their origin have been even less satisfactory. It seems natural to some in any difficulty to say simply that endothelial cells proliferate and produce these cells. But although this unsupported statement has been made the basis of many detailed studies of various infectious diseases and experimental studies, there is not the least actual evidence that it is true.

In the early lesions of leprosy it is not possible to name each and every infiltrating cell. In some rapidly progressing leprous granulations many of the cells are simply large phagocytic cells such as occur in many diseases except that some have engulfed bacilli and become vacuolated while others are elongated or spindle shaped and not distinguishable from fibroblasts except that they lack the fibrils.

Mitotic figures were seen in lepromas by Virchow and by Malassez, who regarded leprosy as a sarcomatous process. Schmidt went to one extreme: "Neoplastic cells may be derived from the glandular, epithelial, endothelial or even fat cells." Philippson, and Havelberg, also saw mitoses, and subsequent observations have varied greatly. When present, mitoses occur particularly at the margins of the lesions in cells of several kinds. Cowdry, Heimburger and Williams, studying lepromas by the Feulgen reaction, noted the absence of thymonucleic acid, and by microincineration they observed variation in mineral contents, particularly a relatively low amount of calcium ash. Reticulin is elaborated throughout the leproma, while the elastic fibers of the corium are destroyed. Milasch reported the formation of irregular balls of newly formed elastic fibers at the margins of nodules, like the hyperplastic elastic tissue in some cases of atrophic dermatitis.

Philippson pointed out that both the lipoids and the bacilli in some cells occur not in the vacuoles but in the intervening cytoplasm. On the

other hand, it has been a routine observation that even small groups of bacilli in young cells occur within vacuoles, although the lipoids are strictly cytoplasmic. Not all vacuoles are occupied by bacilli. Plasma cells, scattered in loosely arranged foci at random through the nodules, are usually accompanied by some lymphocytes.

GLOBI

The masses of bacilli within the tissues are called globi (originally meant by Neisser to designate the vacuoles about the organisms). Cowdry cited Manson-Bahr to the effect that the sizes and numbers of globi present are a factor of the age of the lesion.

In smaller globi the bacilli form conglomerations or bundles arranged in fascicles, the "cigar packs." The shape becomes spherical after enlarging through various irregular forms, a common one being an irregular ovoid form, which Cowdry called a seed globus. The organisms become so closely matted as to appear agglutinated, with individuals often indistinct, while one or more round hollows develop in the centers of some of the larger globi. In old or regressing lesions, degenerating forms are seen to the point of disappearance of bacilli. In fresh smears the globi often fill the vacuole completely, but in sections they are shrunken. Often the vacuole exceeds in size the mass of bacilli, to the point where numerous but scattered bacilli should questionably be called globi.

The presence of a homogeneous material among the bacilli, which stains with several nuclear dyes, was known to all the early students of leprosy. Because the material exhibits also the staining qualities of mucin, it has been called a slimy substance, a conclusion without other substantiation. The botanical term "zoogloea," or "gloea" for short, used by Hansen, suggests a living matrix of the bacilli, an idea equally unfounded. The amount present is closely related to the number of bacilli forming the globus, and large globi exhibit large masses of the material, whereas when the bacilli are not so numerous as to be solidly matted, there is usually none. In old lesions from which bacilli have partly or completely disappeared, this vacuolar material may remain behind, well preserved.

The fluid in vacuoles without bacilli or with bacilli in less than global masses does not react to any known dye. It is not fat, at least not in early stages, and Virchow's statement that the cells apparently take up water is as much explanation as is justified.

The thin delicate lining of the larger vacuoles which separates the vacuole from the cellular elements adjacent is also readily stained by a variety of dyes in no characteristic manner. Berengrün supposed it to be the margin of the endothelium of the lymphatic in which the globus

supposedly lay. It is more prominent with the larger globi, doubtfully existent about small masses of bacilli and absent about simple vacuoles. Those who have argued against the lymphatic idea have found no really adequate explanation of its nature (Denney). Cowdry regarded the membranes about giant globi as remains of investing giant cells.

The larger globi often are not spherical but assume complicated elliptic or ovoid forms, with bulges between adjacent tissue elements, and these in particular have been the source of Unna's claim that globi lie in lymphatics. Cowdry (1940) was particularly interested in what he called giant globi. He acknowledged that all stages of intracellular development from cigar packs to seed globi could be seen. The giant globi occur only in advanced lesions, as a later development. Lie (1894) stated: "Das Charakteristische eines Globus kann nicht die Grösse sein" (Size cannot be a characteristic feature of a globus).

That the smaller masses of bacilli are intracellular can be demonstrated, but the largest, which exceed 100 microns in greatest dimension, often have been assumed to lie free in the tissues. Unna believed that plasma cells surrounded the free-lying bacilli. The large masses often seem to extend or flow a short distance along the tissue spaces, perhaps to have broken out of their original confinements. Multinuclear giant cells are commonly found in relation to the larger globi, as recognized by Rikli, Schäffer, Gurd and others. They often consist of a thin layer of cytoplasm with flattened nuclei, completely surrounding the globus, or they resemble foreign body giant cells. Less frequently they may have peripherally arranged nuclei with more abundant cytoplasm, and in these there may be a few cytoplasmic bacilli in addition to the enclosed globus. It is unusual for giant cells of any size to appear in nodules except in relation to moderate-sized or large globi. Both this fact and the appearance of the giant cells suggest that many are formed only after the globus has reached a considerable size and extended beyond the confines of the cell in which it originated. In occasional lesions or unusual cases, as seen by Ramón y Cajal, Rikli, and Boinet and Borrel, giant cells occur in unusual numbers as a striking feature of the lesions, while their occasional presence has been repeatedly observed by Michelazzi, Dohi, Lombardo, and others. Small multinuclear cells, with two or three or four nuclei, can be found on search in almost any case. Most latter day observers concur in the opinion that these are formed by the fusion of single cells, and Cowdry expressed the opinion that even cells with many bacilli might be included. A rare form of massing of the bacilli radially to form rosettes, described by Wolbach (Gurd), is found much more commonly in rat leprosy (Cowdry).

Controversy Over Lymphatic Harborage of Globi.—A feature of the history of the anatomy of leprosy has been the situation created by the

dermatologist Paul Gerson Unna. He described a method of preparing sections stained for bacilli, which included drying the section completely. From these he concluded that the large masses of bacilli lay in lymphatic spaces or ducts and that in fact the bacilli never occurred in cells but only in terminal *Lymphspalten* (lymph clefts). The cellular response was interpreted as secondary to the growth of the organisms in the lymph spaces; the cells plastered themselves against the organisms and their zoogloea. Unna made no exceptions; in all the organs the bacilli were extracellular, lying on and not in the endothelium of blood vessels or of hepatic sinusoids and restricted in distribution to lymph and blood channels. He was answered by Neisser, Hansen and Touton. Neisser was plainly outspoken in his criticism of Unna, calling his methods useless, his material inadequate and his conclusions precipitate. Unna responded without hesitancy in maintaining his views, answering one of Neisser's objections with words which Neisser had addressed to Kaposi at a meeting in Copenhagen: "The important thing is not the number of cases, but how they are studied." He stated the absolute with total finality, "Die Bacillen liegen in der That niemals in den Gewebszellen" (The bacilli, as a matter of fact, never once occur in tissue cells), and, "Since the new tinctorial era of histopathology there has been too much free diagnosis of 'cells'; leprous histology is testimony of this."

Unna had a number of followers, Leloir, Kühne and a dozen others and particularly Berengrün; none seems to have accepted the totality of Unna's "never." Von Bergmann in 1897 remarked that the controversy appeared to have reached a certain laying aside of weapons (*Waffenstillstand*), with acceptance of most of Berengrün's ideas. Furthermore, at this time Jeanselme (1898) said that Unna described himself as a hardened sinner, still maintaining the position.

The importance of the Unna controversy is that it has colored nearly every subsequent histologic investigation of leprosy in some degree. Unna was in gross error on two points. He misinterpreted the Virchow lepra cell; looking for nuclei within globi, he failed to find them and mistakenly thought that the globi were what Virchow had described as cells. His absolute denial of the presence of bacilli in cells is accepted by nobody; not even Unna's most enthusiastic pupils followed him to this extreme, yet Unna himself, having taken his stand, adhered to it steadfastly, unswayed by argument or demonstration, and without embarrassment. The followers of the lymphatic school adopt an oversimplification of the histology of leprosy as though saying, "The lymphatics tell the whole story."

In 1885 any crevice between tissue elements was referred to by some as a lymph space. But with several in Unna's school any cells enclosing bacilli automatically became lymphatic endothelium. There is no report

in the literature of the injection of the lymphatics of a leprous lesion. The literature on leprosy from the standpoint of pathology is filled with compromising statements where the subject of lymphatics enters, and uncritical acknowledgments of the importance of these structures continually appear. For instance, Muir and others (1923) wrote a long article on leprosy from the standpoint of pathology in which they talked much of lymphatics but conspicuously never mentioned lepra cells. In MacCallum's textbook one reads that bacilli "occur chiefly in the swollen endothelial cells of the lymphatics and blood vessels," embodying a sentiment denied elsewhere. The ghost of Unna has yet to be laid.

Of the relationship of the globi to lymphatics Cowdry (1938) wrote:

> Reconstruction of some of these globi from serial sections show one or more delicate channels leading off the lumen through the side of the globus possessed of the thinnest wall. I have not been able to trace them very far, neither have I been able to find them connected with all globi. The openings are narrow, of the same caliber as the channel and not funnel-shaped. They are rather like lymphatic capillaries.

Perhaps even this was compromising with Unna, for later (1940) he wrote:

> . . . It is not feasible to trace continuity between the investment of a giant globus and the walls of a true lymphatic.

Carter described lesions in lymph channels, as did Hoggan. Doutrelepont is one of those who leaned toward Unna, seeing bacilli in lymphatics to the point of incredibility. Sakurane derived lepra cells from lymphatic endothelium, and Dwijkoff wrote expansively on the role of the lymphatic system. Among the champions of the Unna doctrine, Berengrün (1895) wrote, "The bacillus-thrombus is the primary thing; it acts as a foreign body stimulating the endothelium of the vessel." This is a little different from Unna's idea that the cells were plasma cells (a cell of more than one genus to Unna).

Some leprous lesions will show dilated lymphatics at the margins of foci, which are identifiable with reasonable certainty. Cowdry spoke of having seen bacilli in the endothelium of such vessels, and I have seen them in this situation twice. It is altogether probable that some of the older writers have seen similar lesions, but with the lymphaticists the descriptions have to be well salted before taking. It has been said many times that in the peripheral sinuses of the lymph nodes bacilli never occur in the flat lining endothelium, a pertinent, if negative, sort of evidence (Cowdry) that there is no great tendency of true lymphatic endothelium to become infected.

The observation that infiltrating leprous foci occur along or around cutaneous blood vessels and nerves has led to the statement that this

spread is by way of the lymphatics, which occur richly in these sites. However great the possibility that this is the case, the lesions overgrow and spread beyond the lymphatic wall promptly, and demonstration of the lymphatics themselves is usually impossible. Aleixu described 13 cases of leprosy with acute lymphangitis.

Von Bergmann remarked that it was apparent from every bacillus-rich preparation that bacilli lay free in the tissues. Klingmüller spoke of extracellular branching chains of bacilli covered by endothelium, but Gurd found these extracellular masses to be merely in tissue spaces. Such chains of bacilli differ from the globi masses which Schäffer, like Cowdry, was able to follow through several serial sections. But the only ones that I have been able to illustrate were extending between fat cells, unrelated to endothelial or other cells and connected with masses of bacilli in nearby cellular infiltrations.

Leprosy of the lymph nodes is histologically like that of the skin, with the formation of vacuolated cells and globi. The regional nodes are regularly involved, but the visceral nodes seem to escape except when they drain a leprous liver or other involved organ. The bacilli and cells are found earliest in the cortex but may increase to replace the whole node, without spreading into the tissues beyond. Unna Jr. and Lowe (1939) described tuberculoid changes in lymph nodes.

ACUTE REACTIONS; ALLERGY

No formal studies of the acute phases of leprosy from the standpoint of histology appeared until lately (Stein, 1939; Büngeler and others; Ermakova, 1940; Rabello Jr.). Stein studied lesions twelve hours, one day and two, three and four days after the beginning of the reaction. Even at twelve hours he found collections of lepra cells in deeper layers containing lipoid and many bacilli, and perivascular cells developed in the course of a few days into typical lepromas. Fibrinoid swelling of connective tissue fibers, which were yellow with Van Gieson's stain, was seen after twenty-four hours, with various acute changes in small vessels, hemorrhages and leukocytic extravasations. He attributed this to a hyperergic inflammation akin to the Shwartzman phenomenon but recognized that many of the apparently new lesions were old ones made evident by the acute reaction. Ermakova described a fatal acute reaction with hemorrhagic changes in the lesions, degeneration, and want of acid-fastness of the bacilli in reactive nodules, and I have seen a similar picture with widesperad acute necrosis of all the infiltrations and with colonies of non-acid-fast organisms, apparently lepra bacilli, in the lymph nodes. In general, in acute phases the bacilli occur in extremely numerous but small separate intracellular bundles and, in sections, lack individual distinctness (Fernandez). Büngeler and colleagues observed the circulatory phenomena in connection with the acute reaction, edema

and fibrin being present in the tissues in early stages, and likewise considered this evidence of an allergic state. Later eosinophils and leukocytes appeared with decreasing numbers of bacilli, and a third healing phase was described. They have also divided acute reactions into types, according to the types of lesions. Traditionally, the acute or lepra reactions are accompanied by the appearance of new lesions and the activation of old ones which may have lain dormant months or years. They vary from the rare profound systemic reactions, which lead to death, to the mild ones, in which the histologic changes consist of nothing more than the suggestion of rapidly advancing lesions. The changes in the acute reactions of tuberculoid leprosy, described by Wade, Büngeler and a few others, are largely of this sort, perhaps with the presence of bacilli previously not demonstrable, although some of the circulatory phenomena have been described in connection with them.

The necrosis taking place in leprous lesions in relation to acute reactions is not uniform and does not appear to be a regular feature. The ulcerations which so commonly occur on the crests of acutely inflamed nodules doubtless arise from small superficial areas of necrosis. In deeper nodules suppuration with fluctuancy but without ulceration is sometimes apparent, and I have seen a few instances in which this necrotic material was *not* laden with bacilli and in which small ulcers occurred on the surface of old, almost obsolete nodules without any increase in the few, poorly staining organisms present. In old long-staining lesions in which the tissues, if not the patient, are approaching mortification, secondary infections may lead to broad putrid sloughs, which in the extremities will sometimes correspond with areas of total anesthesia. On the "trophic ulcer" of leprosy, that *horrendus malus morbus,* the histologic literature has been kind by saying little. Histologically, it is like the bed sore, a first cousin. *Erythema nodosum* (Chala) is another phenomenon not too uncommon in leprosy, which may have an allergic significance, together with some bullous or pemphigoid lesions.

Pigment Changes.—"Leprosy," said Gilbertus Anglicus in the thirteenth century, "is an infection or alteration of the natural color of the skin to an abnormal or uneven color with the equality of flesh." The mediaeval German poet, Conrad von Würzburg (via Babes and Virchow) wrote of a leper:

> Des Leibes Farbe, sonst zu schauen
> In früherer Zeit so licht und gut,
> Sie war viel röther noch den Blut,
> Und gab so sonderbaren Schein.
>
> (The color of the body, which
> In earlier days had been so clear and normal,
> Was now much redder than that of blood
> And gave a most peculiar appearance.)

While Holcomb shows that Gilbert and other mediaeval writers mixed leprosy in with syphilis and other diseases, the color changes in leprosy may be as dramatic as they describe. The most common is the reddening of the lesions which occurs with acute reactions, while some macules exhibit from the first nothing but depigmented patches. In some of the more florid lesions there is a period beginning with the height of activity during which marked hyperpigmentation occurs over the active area.

In the depigmented patches Henderson noted no change in the melaniferous apparatus other than that the pigment was lowered in amount in its normal sites, as shown by silver stains. Muir (1923) saw little but increases or decreases in amount comparable with the clinical evidences. Wade, Stein and many others have agreed that the pigmentary changes are secondarily brought about, either through local stimulation during acute phases or through atrophic changes, associated with neural disturbances.

LEPROUS CHANGES IN SKIN

Sweat Glands.—Since 1860 it has been known that infiltrations of the sweat glands are a prominent occurrence in cutaneous lesions of all kinds, the larger infiltrations separating the coils and often preserving them embedded in solid lepromatous tissues. The involved glands do not respond to pilocarpine as do normal glands, with a profuse production of sweat.

Hoggan's description of the changes in sweat glands is confused by his erroneous ideas of the nature of leprosy. Touton produced a beautiful illustration of a sweat gland with numerous bacilli in the gland cells and lying free in the ducts. Michelazzi expressed the belief that such bacilli were thereby eliminated from the body. Spillman and others found them here rather commonly; Ishizu, rarely. Des Essarts and Lefrou (1937) described the various infiltrating cells in detail, as well as various degenerative changes in the glands proper, and expressed the opinion that bacilli passed through unbroken glands into the sweat. Although it is argued by others that this is an important basis of the spreading of leprosy, infection of the gland cells is not a routine occurrence.

Sebaceous Glands.—The involvement of the sebaceous glands is of much the same order with bacilli rarely if ever found therein, as described by Cornil and Babes, and Ishizu, while degenerative, pressure and atrophic changes are the rule in advanced lesions, which also affect the hair follicles. In some tuberculoid lesions I have seen the sebaceous glands more frequently the centers of granulomatous foci than the sweat glands.

Epidermis and Hair Follicles.—Cornil and Babes, Touton, Thoma, and many others since, observed bacilli in the epithelial cells of hair

follicles. Only a few, e. g., Guttmann, have failed to see them here. Bacilli within cutaneous epithelial cells may be observed especially among cells near the base of the hair follicle and in the epidermis near ulcerated margins of involved areas or elsewhere related to regenerating epithelium. At the root of the hair, the cells surrounding the papilla are often involved, while the papilla itself with its rich vascularity may be diffusely leprous. The epithelial cells infected are sometimes those of the bulb at the root forming a new hair, or those of the external sheath of the root nearby. It commonly happens that all or a group of hair follicles in a particular area be similarly affected, although other lesions, equally heavily laden with bacilli, show no invasion of epithelial cells. Bacilli may be found also along the hair shaft, but it frequently happens that the hair has been shed, and the attempt to regenerate a new hair has been unsuccessful. Degenerative or atrophic changes in hair follicles without bacillary invasion are more common.

The epithelial cells containing bacilli show some vacuolation but do not accumulate lipoid, and bacilli, although numerous, do not form in masses as globi. Muir and Chatterji (1932) have suggested that bacilli escape to the surface through the interstices between the epidermal cells, and Klingmüller noted that typical lepra cells were not formed from the epithelial cells. He and various others have shown that bacilli may be demonstrated in epithelial cells scraped from the surface of many nodules. The importance of the "follicular apparatus," stressed by Muir (1936) and Stein (1940) as affording a starting point for leprous foci, depends on the vascularity of the papilla of the hair follicle, not on infection of epithelium.

Lipoids.—The earliest stain for lipoid to be used was osmic acid, reported by Hansen (1871) and shown to be capable of staining the bacilli. Iwanowsky's fatty changes seem to have been inclusions of neutral fat from fat tissuees in nodules. Philippson (1893), using osmium, described finely granular lipoid in the walls of vacuoles or in the cytoplasm of the bacillus-containing cells, showing that a small amount of cytoplasm stretched between the vacuoles was thus demonstrated by osmium when not apparent otherwise (Storch). Mitsuda showed that sudan III stained the lipoids well and the bacilli slightly. MacCallum (1916) observed the presence of much fat in leprous nodes, and found it not doubly refractile. Salvioli confirmed this, but Cedercreuz found both neutral and doubly refractile fat in 2 cases. This has not been confirmed by Herxheimer or by many others who have since agreed on its absence.

Mitsuda employed the Fischler, Ciaccio and Smith methods as well as nile blue and sudan, as did Herxheimer, finding the lipoid stained in some manner by all; sudan gave it not the bright red of neutral fat but a

brownish color. He concluded that it was lipoid of indefinite composition containing fatty acid, while Herxheimer said that the Smith-Dietrich method showed it to be a mixture of esters of cholesterol, glycerin and fatty acids containing some free fatty acid.

The lipoid appears in the bacillus-containing cells as soon as the bacilli. At first it is strictly in the cytoplasm of the cells, the vacuoles being quite free, but it increases with the age of the lesion, gradually compressing the vacuoles; old lesions may be so filled as to give the tissue a greasy texture and then the tissue stains brilliantly with sudan in the gross.

Verrucous Lesions.—De Souza Araujo (1937) reported 3 cases in which he felt the verrucous lesions might be due to an added fungus infection, which he was unable to demonstrate. Braga contributed 2 more examples of this. The changes in the skin, marked acanthosis with edema and nonspecific chronic focal inflammation in the dermal papillae, correspond to the disease which American textbooks designate as dermatitis vegetans. I have seen a dramatic example of this, with warty lesions covering most of the lower parts of the legs, marked by much putrid bacterial surface growth over the unbroken but anesthetic skin.

LESIONS OF BLOOD VESSELS

Although Uhlenhuth found bacilli in the intima of the aorta and in that of the jugular vein, the vessels involved are principally those associated with lepromatous lesions of the skin (and nasal passages and testes). In the skin, vessels of any size may be infected in one way or another, and virtually any cell, endothelial, smooth muscle or connective tissue, may show bacilli.

Bacilli in endothelium were shown by Cornil and Babes, and Touton described the organisms in intima, media and adventitia. Rikli, Gurd, Schäffer and many others have shown bacilli in capillary endothelium, and when present there they are usually observed in endothelial cells of both arterioles and the venules supplying them (Fite); such invasions are extensive in some areas, but absent from others.

The endothelial cells containing organisms become swollen and even vacuolated, and although fair numbers of bacilli develop, there is no lipoid, and the organisms do not form solid globi as in the lepra cells. Philippson found the bacilli in capillaries parallel to the long axis of the vessel, lying near the nuclei, but the statement is correct when only few bacilli are present. Infected cells may extend as a complete inner sheath into moderate-sized veins (Sakurane).

Perivascular leprous foci are so common that the dividing line between adventitia and leprous infiltration is obscure, and although it is proper to speak of a general infiltration of the adventitia, intimal or endothelial

involvement is rare compared with this (Glück, 1898). Philippson noted that the bacilli in the endothelium stain better, and Henderson's illustration of this, as well as those of Riecke, Herxheimer and Klingmüller, indicates that many of the intimal and endothelial lesions are comparable to those of the epithelium: They occur in older nodules as a secondary invasive phenomenon.

Infiltration of larger vessels appears to take place via the vasa vasorum, but smooth muscle fibers containing bacilli have been seen only in small arterial branches. Large veins of the extremities rarely show leprous thrombophlebitis (Philippson, 1899), although the general absence of thrombi even from most heavily infected blood vessels shows how little cellular injury the lepra bacillus provokes. Doutrelepont and Wolters found bacilli in the clots in large vessels. Rivelloni made capillaroscopic studies of the skin, and Ota and Sato found obliterative endarteritis in tuberculoid lesions.

LESIONS OF NERVES

The involvement of the peripheral nerves is generally considered an ascending infection from the skin. Little is known concerning the involvement of the sensory nerve endings with the exception of Pacini's and Meissner's corpuscles. Hoggan before the lepra bacillus was known described obliteration of the pacinian bodies, believing this to be the result of nerve atrophy. Sudakewitsch later gave an extensive description of the bacillary invasion of the pacinian corpuscles, observing that the bacilli lay between the lamellated plates and along the vessels; when bacilli were numerous, there were granulation cells filling a central cavity. The central nerve fiber was always atrophied. Older processes showed atrophy and fibrosis of the corpuscle with disappearance of the central nerve fiber. As to Meissner's corpuscles, Dacco noted their destruction in a case of anesthetic leprosy. Saijo and Takino showed that many normal corpuscles were to be found, while the greatest damage resulted where bacilli were most abundant; they also found degeneration of nerve endings in muscle fibers. Later Takino and Miyake showed masses of bacilli arising in Pacini's and Meissner's corpuscles and in taste buds. Askanazy proposed that leprosy primarily involves the terminal nerves, whence lesions are neurolepromatous in origin. Torssujew studied silver impregnations of the fine terminal nerve fibers in which he saw breaks and nodular thickenings, some of which apparently represented attempts at regeneration. MacCrae noted "the separation of the two sensations of touch and pain by leprosy." In late years the differentiation of sensations of heat and cold from those of pain or touch effected by the anesthesia of leprosy has received much attention, but the anatomic basis of these peculiarities is obscure.

DeBeurmann, Gougerot and Laroche wrote of a patient with extensive leprosy of four years' duration but with cutaneous sensation intact, and Leloir (1886) said "on a certainment trop exaggéré cette constance de l'anesthésie" (certainly this constancy of anesthesia has been much exaggerated). I should be inclined to dismiss these observations except for the experience of an autopsy in a case in which there was extensive bacillary infiltration of all the cutaneous nerves of the face, where the infection was heaviest, and sensation was unaltered. For this, perfect preservation of nerve ending seems necessary though many nerve fibers were destroyed.

Except for the apparatus of Rezzonico, the Schmidt-Lantermann incisura and the nodes of Ranvier, bacilli have been demonstrated in every part of the nerve fiber. It is generally accepted (Ermakova) that the numbers of bacilli present correspond roughly to the numbers in the cutaneous lesions and that the nerves associated with nodules may be as rich in bacilli as the lepromatous infiltrations themselves. Virchow saw lepra cells enclosing individual nerve fibers. According to Cornil, Babes was the first to demonstrate bacilli in leprous nerves in 1881.

The leprous lesions of the small branches in the skin are the same as those of the main nerves. In the average more or less active lepromatous lesions the nerves are found infiltrated by bacilli and cells, with degeneration of myelin sheaths and axis-cylinders, together with proliferation of the connective tissue of the perineurium and the endoneurium. The picture as a whole is complex, and the thick ulnar nerves described by Danielssen, Virchow, Arnott, Arning, Langhans, Arning and Nonne, and others are not only the result of old lesions but the product of both progressive and regressive changes taking place simultaneously.

That organisms occur inside the myelin sheath, i. e., in the axis-cylinder, has been specifically stated by Lie (1894), Uhlenhuth and Takino. Others have employed the statement "bacilli occur in nerve fibers" (Wynne; Guttmann; Arning; Ermakova) but have not specified the axis-cylinder or the myelin sheath. Although Lie stated that stains for the myelin sheath will also stain lepra bacilli, this is not universally true, especially if paraffin rather than celloidin[2] sections are used. I have seen a case of acute neuritis in which the the central canals normally containing axis-cylinders showed numerous bacilli, often in solid masses distending them and smoothly enclosed by myelin. Although Sokolowsky presented the opposite view, that bacilli never occur in nerve fibers, and Kellogg in teased preparations found the organism only on the surface of nerve fibers and not within, it is possible that actual growth along axis-cylinders is more common than has been proved. Higher up in the main nerves it is often possible to show single bacilli in axis-cylinders.

2. Celloidin is a concentrated preparation of pyroxylin.

Dejerine and Leloir used osmium to show degeneration of myelin in 1881, as did Hansen, Babes and some others shortly thereafter. A few years later, with the introduction of Weigert's method, degeneration was shown by that method. Actively leprous nerves usually show every degree of demyelination in one or another group of fibers. In small branches in the skin the myelin is often completely gone, while the bacilli appear to be increasing in numbers. Although there are many statements that bacilli may be found more readily in terminal nerve branches than elsewhere in the skin in mild leprosy, I have seen only a rare instance in which this has been so.

Bacilli have been described in the myelin sheath by Takino, with globi arising there. Nonmyelinated nerves usually are found uninvolved, although Takino, and Ermakova, showed the usual leprous changes in the sympathetic vertebral chains and ganglions in cases of the nodular form with extensive involvement of the nerves. Takino also found bacilli in the vagus nerve, an isolated observation.

The presence of bacilli in Schwann cells has been claimed by Sokolowsky, Uhlenhuth and a host of others and denied by Cowdry (1940). Multiplication of the Schwann cells as seen by Shaw is a common finding, attributable to wallerian degeneration. The identification of Schwann cells in some leprous nerves is a doubtful possibility, particularly when other mononuclear cells have infiltrated the involved nerves widely.

There is marked hyperplasia of the fibrous cells of the perineurium, and although an increase of endoneurial connective tissue cells is not so marked, a diffuse increase in endoneurial collagen is extensive (Woit). Bacilli have been found in the connective tissue cells from early days (Hoggan; Babes, 1897; Arning, 1884; Rikli; Wynne), usually singly or as small compact bundles without vacuolation, lying close to the nuclei. The perineurium becomes a thick collar of the nerve, quite cellular at first, but contracting about fibrous nerve bundles, in which a few normal fibers may persist.

There are always some infiltrating cells—lymphocytes, plasma cells, mast cells and mononuclear cells. The last may contain bacilli, with development of globi. In the early stage of their development into lepra cells they often present the appearance of simple phagocytes, and they and other infiltrating cells are found particularly about blood vessels. The organization of these cells to form solid leprous nodules is infrequent, although Grieco (1938) said that in cases of the nodular form of leprosy the lesions of nerves result particularly from bacillus-laden vacuolated cells producing compression of nerve fibers. Mitsuda and Ogawa described lepromatous changes in "certain" cases, and Lowe spoke of having seen them, as I have, rarely. But for the most part the cells infiltrate the nerve along vascular pathways and along clefts between nerve fibers.

Dejerine and Leloir expressed the belief that the cutaneous lesions might represent spread from the nerves, but Dehio (1889) and Gerlach proposed a now classic diagram of the spread from the skin to the nerves and from one nerve to another where branches join. Gerlach emphasized the possibility of metastatic nerve lesions, also favored by Mora Guarnido; Muir and Chatterji (1936) suggested that bacilli might pass up the nerve via the cutaneous neurovascular plexus, without producing lesions of the skin, while they, and Takino also, proposed that spread along the nerves was by way of the lymphatics of the nerves, an idea flatly contradicted by Maximow's, ". . . . these vessels have not been found . . . in peripheral nerve trunks." Raynaud's bodies and other similar degenerative lesions (Arning and Nonne) occurring above the sites of activity in old cases are not directly or characteristically related to leprosy, if at all. The perineural spaces which are sometimes illustrated by carcinomatous infiltrations about nerves are obliterated by the proliferation of connective tissue in leprosy.

Abscesses of Nerves.—Combemale and Marestang described caseous cavities inside leprous nerves, distending the nerves to various degrees, with bacilli not demonstrable in some but common in others (Marestang). Arning (1899) described an early abscess of a nerve. Lie (1905) mentioned occasional abscess formation with calcium deposits in the ulnar nerve at the elbow, and Muir (1924) saw a typical lesion, while Lowe (1929) contributed 19 examples, with others being added by Wade (1934), Lowe (1934), Ota and Sato (1934), Schujman, Chatterji, Bosq, Grieco and Nolasco. These have consisted of elongated caseous masses within the perineurium, particularly that of the ulnar nerve above the elbow, sometimes rupturing through the nerve casing. Histologically, they show large amounts of central caseous material surrounded by a zone of typical tuberculoid granulomatous tissue with large epithelioid cells and giant cells. Bacilli are usually absent and rarely common. Schujman suggested that an allergic state contributes to their formation. Calcification appears to follow the caseation as it does in tubercles.

Central Nervous System.—The older literature of leprosy deals extensively with a possible relation between leprosy and syringomyelia, or Morvan's disease (Steudener; Langhans; Pestana and Bettencourt; Woit). Lie (1905) dismissed it completely on the basis of his own studies. Many others who studied the central nervous system in leprosy failed to find changes akin to those of syringomyelia.

A second confusing finding of former days was degeneration in the posterior columns of the spinal cord in clearcut cases of leprosy. Arnott expressed the opinion that it might be of a postmortem nature, but later writers attributed the degeneration to leprosy. The possibility of

syphilis as a cause of such degeneration was given no thought by Colella and Stanziale, Looft, Jeanselme and Marie, or Woit. Lie (1905) further described such lesions, but this was the critical date ne plus ultra, and in 1930 he abandoned the former position. Others, e. g., Storch and Babes (1897), found no changes in the spinal cord, and Vilde recently concluded that the only lesions of the spinal cord are those secondary to arteriosclerosis, while Ermakova (1936) found the central nervous system wholly normal.

The occurrence of bacilli in the spinal, gasserian and other ganglions in cases in which there was heavy infection of the nerves is well established (Sudakewitsch; Lie; Uhlenhuth; Babes; Natali). Rarely bacilli have been seen in neurons of the anterior horn of the spinal cord (Andriani), in Purkinje cells (Uhlenhuth) and in the pia (Doutrelepont and Wolters). There is the curious isolated case of de Beurmann and others of leprous meningitis and pleuritis.

LESIONS OF THE RESPIRATORY TRACT

Nose and Throat.—Leloir (1885) described leprosy of the nose and pharynx as being usually a broad superficial infiltration, and Glück (1897) indicated that in many cases the lesion remains flat and infiltrates the deeper tissues only to a moderate extent. Elevated or projecting nodules may also be found but less frequently than the flat lesions and only in cases of well advanced nodular leprosy. Hollmann found the nose infected in 89 per cent of cases of nodular leprosy, 66 per cent of cases of mixed and 45 per cent of cases of anesthetic leprosy, and many similar compilations have given comparable results. In the earlier cases Akamatzu showed that the apparently intact nasal mucosa may contain numerous leprous infiltrations crowded with bacilli.

Wade and others have shown that a common early site of leprosy of the nose is the cartilaginous-bony juncture of the septum, the cartilaginous septum often being destroyed with resulting perforation. Glück saw infiltration of the perichondrium and of the cartilage cells with bacilli, though the latter was "not an everyday experience." Both he and Akamatzu found vascular lesions rather common and involvement of nerves the rule.

Further involvement of the upper air passages may become most extensive or even diffuse. The epiglottis is easily destroyed, and von Bergmann noted that an area of efflorescence of the mucosa ulcerated much more readily than one of the skin. Laryngeal lesions destroy the vocal cords, and resulting fibrosis or granulomatous masses may necessitate tracheotomy (Breda, 1908). In the lower areas normally covered by columnar epithelium, squamous metaplasia of the epithelium attempting to recover ulcerated areas is common (Lie). The mucous and

serous glands become infected, with bacilli in secretory cells and ducts, and metaplasia of the epithelium of these ducts follows regularly. Extension into main salivary glands is, however, rare. Of the 5 heavy infections of the larynx that I have seen, all were in persons dead of advanced pulmonary tuberculosis, and the laryngitis was a mixed tuberculous and leprous process with both diseases flourishing and intermingling.

Lung.—In the older literature there is much confusion between tuberculosis of the lung and so-called leprosy of the lung (e. g., the articles by Bonome, Délépine and Slater, Riehl, Babes and Moscuna, and Arning [1898]). Fambri reported a case he believed to be one of pure leprosy of the lung, yet his case, Bonome's and the case reported by Babes and Moscuna were almost surely simply instances of tuberculosis with plentiful bacilli. Hansen and others had doubted the occurrence of such a disease as pulmonary leprosy, and Doutrelepont found only tuberculosis. Scagliosi argued against pulmonary leprosy, and Schäffer considered it most rare. The case of de Beurmann and co-workers is not free from suspicion.

Jeanselme (1911) recognized minute leprous foci in septal walls, some within capillaries, but doubted that any other change occurred in the lung in leprosy. Sugai reported something similar, having found occasional bacilli in otherwise normal lungs. Mitsuda (1936) stated:

> . . . The bacillus is to be seen in the histiocytes in the interstitial tissue, within endothelial and perithelial cells of the blood vessels, and in the dust cells. There are also groups of lepra cells that are sometimes from 0.01 to 0.1 mm. in diameter. The dust cells, heavily laden with coal pigment, change into the vacuolated cells upon the entry of the bacillus and stain orange by Sudan III.

Kobayashi saw similar lesions, and Tajiri described rare minute septal and subpleural foci, particularly as demonstrated by fat stains. In the majority of cases reported, no lesions at all have been found.

LESIONS OF OTHER ORGANS

Liver.—Leprosy of the liver is transparently the result of vascular seeding. Rake (1892) wrote that he "had never seen any visceral macroscopic changes which could with certainty be ascribed to leprosy." Sabrazès said, "Properly speaking, leprous nodules are not found in the liver." Müller and Mertodidjojo found gross lesions always to be tuberculous and not leprous.

Kupffer cells containing bacilli are a constant finding in the liver in cases of nodular leprosy (Hansen; Neisser; Guttmann; Babes). Mitsuda pointed out that bacilli in Kupffer cells are often well preserved in form and tinctorial properties while those in other hepatic foci are fragmented and beaded, the difference being due to a difference in ages.

The Kupffer cells readily become vacuolated and, according to Bertelotti, tend to develop into lepra cells but do not complete the process. They may contain large masses of bacilli, as in the case of Sabrazès, or only a few. In some cases it appears from the widespread diffusion of small numbers of organisms in single cells, and the infrequence of larger foci that few of the bacilli phagocytosed by the Kupffer cells from the blood stream reproduce further. Larger foci may develop from the Kupffer cells to become slightly elongated and distend the sinus, a delicate fibrous framework developing with reticulum and capillaries.

Similar foci, often called miliary lepromas, develop commonly in two other positions, the portal areas (Dehio, 1876) and along the walls of emissary veins. It is usual to find these at autopsy with rather few bacilli and a good deal of lipoid, often obsolete. Their limited individual size also speaks for a brief period of activity and ready regression.

Salvioli, Andriani, Sugai and de Beurmann have attributed cirrhotic states to leprosy. However, there is no good reason to suppose that these are other than Laennec's cirrhosis occurring independently in patients with leprosy. The presence of bacilli in hepatic cells has been recorded by Andriani, Leloir, Rikli and Jeanselme, but Mitsuda (1936) stated my own experience: "Rods that simulate leprosy bacilli are often found in liver cells, but they are nothing but fat or bile pigment crystals."

Spleen.—The lesions of the spleen are comparable to those of the liver, being similar in size, or smaller, and of the same character. Neisser (1886) noted that they were particularly found about blood vessels. The foci are chiefly like those in the Kupffer cells, occurring where small vessels or capillaries open into the pulp, in or at the margins of malpighian bodies and along small trabecular vessels. In light involvement, as in the case reported by Dwijkoff, there may be little more than scattered vacuolated cells with a few bacilli, which it would be impossible to demonstrate without staining for acid-fast bacilli or fat. Although in extreme involvement innumerable foci are found occupying a good part of the tissue, heavy bacillary infection, as in the case of Sabrazès, is uncommon. Tuberculous lesions are so often seen in leprous livers and spleens that minute leprous foci may develop in the outer epithelioid cells of unquestionable tubercles.

There is a much larger literature on leprosy of the liver and spleen than I have indicated. Biehler wrote a monograph on leprosy of the spleen, and Schäffer reviewed visceral leprosy in 1898, as did Jeanselme in 1900. Mostly volume has been added to the subject since, except that Pineda called attention to some cases of cutaneous leprosy apparently without bacilli in which persistent search revealed a few organisms in nerves and viscera.

Testis.—Whereas leprosy damages the liver and the spleen to no important degree, it frequently destroys the testis as a functioning organ (Schäffer). Cornil and Babes saw large numbers of bacilli in the testis, and Leloir observed that the testis was almost always involved soon or late in nodular leprosy. Neisser (1881), Storch and Rikli saw rich bacillary infection of the testis between the tubules only, but it has been demonstrated that the organisms may proliferate in the tubules, in the spermiogenic cells (Kinoshita; Kobayashi) and perhaps in the Sertoli cells. Hansen (1893) found the bacilli in the tubules, both within and outside the cells, producing huge irregular masses that almost filled the tubular canals.

Thoma showed that the interstitial infiltrates consisted of the usual various cells, lymphocytes and predominantly those which develop into typical Virchow cells. They lead eventually to a high degree of sclerosis (Natali), with atrophic tubules remaining as islets in dense scar tissue, or there is diffuse fibrosis between hyaline tubules, with sometimes scattered islands of Leydig cells. The blood vessels and nerves may be affected, but in the testis proper the process rarely becomes lepromatous with the formation of nodules. It is usually a diffuse interstitial infiltration intense in degree but thin in volume, limited by the tunics of the organ.

Bacilli may occur in the epithelium lining the ducts of the rete, rarely in that of the first part of the epididymis, although the neural infiltration extends well into the epididymis and occasionally small lepromatous nodules are formed along the pampiniform plexus.

Bones.—There are two common changes in the bones in leprosy. One of these is the presence of scattered minute cellular and bacillary foci in the red marrow, which are comparable to those seen in the liver and the spleen (Babes). Gass and Rishi found the marrow infected in 17 of 20 cases of nodular leprosy and free from bacilli in 48 cases of neural involvement. The other common change is the absorption of the terminal bones of the extremities, particularly the phalanges. Study of these atrophic changes by roentgenograms (Harbitz; Dubreuilh; Honeij) shows that the bones undergo a peculiar type of atrophy and resorption, quite independent of nodular activity (Hirschberg and Biehler), in which whole phalanges waste and vanish. The marrow becomes adipose (Haüpl), the bones become very soft from loss of calcium, and resorption by osteoclasts follows leisurely or is not conspicuous. The normal trabeculation collapses with little change in the basic structure. These resorptions occur without infection of the bones by lepra bacilli or by secondary infecting organisms, although purulent osteomyelitis is a common complication.

The relation of these alterations of bone to the anesthesias accompanying them has led to their designation as trophic changes. Yet in nearly all writings there appears dissatisfaction with this as the complete explanation, "These bone changes seen so early and which are so gradual, particularly in the nodular type of leprosy are not . . . sufficiently accounted for" (Honeij).

Actual leprous infiltrations of bones, rare enough to be a most unusual experience, have been described by Hallopeau and Lebret, Rath de Souza, Mitsuda and Ogawa (in the form of cranial periostoses), Hirschberg and Biehler, and Sawtschenko. The last in his case saw bacilli in osteoclasts, in haversian canals and endothelial cells and in the periosteum.

Eye.—The lesions of the eye have attracted much attention since Bull and Hansen published their book describing punctate keratitis, spreading conjunctival nodules and some of the secondary changes. Direct extension of leprous lesions of the skin to the conjunctiva and thence to the cornea is an important mechanism by which the eye is involved. As described by Babes and Levaditi, the bacilli pass from the limbus to the cornea, later penetrating the ciliary body and the iris, with ulceration and perforation of the cornea possible. The lens is not invaded but may be absorbed. The bacilli pass from the ciliary body along the ciliary nerves to the equator of the eye, but the posterior part of the eye is not invaded. Franke and Delbanco described the changes seen in a case of leprosy of the milder type in which bacilli occurred at the angle of the anterior chamber, particularly about blood vessels in the iris and the ciliary body, but suggested that the eye might become involved by the hematogenous route (Borthen and Lie), with the occurrence of numerous minute granulomas scattered throughout the uvea.

The corneal involvement, keratitis punctata superficialis leprosa, as studied by Philippson, Borthen, Masuda, Breda (1913) and others depends on the spread of bacilli between the connective tissue plates of the cornea. The bacilli are found mostly within but also outside cells, globus formation being rare, even though the organisms are fairly numerous. Masuda saw the organisms in spindle cells under Bowman's membrane or between it and the epithelium. The cornea apparently remains avascular in spite of the leprous infiltrations.

Secondary lesions of the eye of wide variety, such as the chorioretinitis described by Bistris, may follow the leprous process, yet there is no tendency of the infection to spread into the retina or the optic nerve. Although Lie found bacilli in the optic nerve, it seems clear that this invasion is not comparable to that in the peripheral

branches of the somatic nerves. The lesions of the uvea may become granulomatous like those of the skin.

Gastrointestinal Tract.—Von Reissner described leprous lesions of the large intestines in 3 cases, but to his report and other reports of this nature by Danielssen and Boeck, Arning and Monastirski there attaches suspicion, especially since von Reissner did not think there was too much distinction between leprosy and tuberculosis histologically.

Kidney.—Bacilli rarely lodged in glomerular capillaries were observed by Rake, and the observation was confirmed by Nonne, Wynne, Brutzer, Sokolowsky, Sugai and Kobayashi. Here they seem scarcely to produce lesions.

Ovary.—Glück and Wodynski reported 6 cases of ovarian involvement with interstitial lepra cells containing bacilli and also much brown pigment. Gentilli saw the same. I have seen a single ovary with a few leprous foci, and in view of numerous negative findings the process here must be considered unusual.

Mammary Gland.—Powell claimed that of 302 males with leprosy 79 per cent had enlarged nipples; he considered the enlargement of the nipples an important diagnostic point. Muir (1934), Pinnetti and Sapo Baretto described enlargement of the male breast (gynecomastia) associated with or dependent on atrophy of the testes. Tissi contributed more material, and Baptista (1937) reviewed the literature, giving new examples.

Babes found bacilli in the female mammary gland. Sugai found bacilli in the milk of 2 nursing mothers. One of these was found to have bacilli only in smooth muscle cells of the nipple, at the poles of their nuclei; the other, in lepromatous infiltrations of the capsular connective tissue of the gland.

Placenta.—Sugai found bacilli in the placenta and in the blood of the heart of a newborn fetus, but the most interesting finding is that of Pineda, of whose 104 placentas 55 showed bacilli on smear.

Thyroid, Parathyroid, Pineal, Adrenal and Pituitary Glands.—The adrenal gland not infrequently shows small miliary leprous foci in cases of heavy infection, like those of the liver, occurring near the vessels or at the margins of the cortex and the medulla. In the other glands of internal secretion Pinnetti and Natali showed in several cases complex nonleprous changes, probably associated with testicular atrophy. Muneuchi's analysis of 45 parathyroid and 10 pineal glands showed foamy cells (not necessarily with bacilli) in 37 of the parathyroid and all the pineal glands.

ANOMALOUS OBSERVATIONS

There are inevitable curiosities which turn up in so multiplex a disease as leprosy. Askanazy likened leprosy to von Recklinghausen's disease, and Johannsen and McCreary found numerous bacilli with globus formation in the neurofibromatous neoplastic cells of the lesions of a patient with both diseases. Black saw bacilli in cancer cells in 2 lepers. Ciaccio reviewed the subject of keloids in leprosy. Pautrier wrote of a case in which there were multiple cutaneous hematomas filled with organisms. Lara's theory of ptomaines and leprosy belongs with Jonathan Hutchinson's doctrine of fish-eating and Webb's curse of vaccination as spreading the disease.

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Notes and News

Appointments, Deaths, Etc.—David J. Davis retires next September 1 as professor and head of the department of pathology, bacteriology and public health, and as dean, of the University of Illinois College of Medicine. He became professor of pathology in 1914 and dean in 1925.

Martin H. Knutsen, professor of bacteriology in Pennsylvania State College, died February 6, 55 years old.

Eugene Markley Landis, professor of internal medicine in the University of Virginia, has been appointed professor of physiology in the Harvard Medical School, Boston, succeeding Walter B. Cannon, retired.

David L. Coffin, of the department of veterinary pathology of the University of Pennsylvania, has been appointed Herbert Fox memorial fellow in comparative pathology by the Zoological Society of Philadelphia.

Institute of Medical Research.—The Institute of Medical Research of the Toledo Hospital, Toledo, Ohio, was dedicated March 27. The institute, established and maintained by a legacy of the late Frank Collins, will be under the direction of Bernhard Steinberg, the director of the laboratories of the Toledo Hospital.

Society News.—The 1943 officers of the Society of American Bacteriologists are Rebecca C. Lancefield, president; I. L. Baldwin, vice president; W. B. Sarles, secretary-treasurer.

The American Public Health Association will sponsor a three day Wartime Public Health Conference in New York city, October 12, 13 and 14 in connection with the seventy-second annual business meeting of the association. The conference will be devoted exclusively to wartime emergency problems of public health.

Book Reviews

Autonomic Regulations: Their Significance for Physiology, Psychology and Neuropsychiatry. Ernst Gellhorn, M.D., Ph.D., professor of physiology, University of Illinois College of Medicine. Pp. xii and 373, with 80 illustrations. Price $5.50. New York: Interscience Publishers, 1943.

Throughout all of Professor Gellhorn's writings there is an undercurrent of philosophy that is at one time highly illuminating and at others obscure. The present volume begins with a quotation from Sherrington stating that physiology "aims at giving reasoned accounts of the acts of an organism in respect of their purpose and use to the organism *qua* organism. This may be called a teleological aim, yet belongs to a teleology not foreign to the scope of natural science." Professor Gellhorn seeks in the present volume to present "an organismically oriented" system of thinking, and one of his chapters is entitled "Contributions to an Organismic Physiology." This implies that "every adaptation is an integration," and Professor Gellhorn intimates that the reactions of the body to anoxia, asphyxia, hypoglycemia and other conditions which involve the autonomic nervous system illustrate the essential unity of the body for the reactions in question and tend to restore the body to the original condition. Thus the autonomic nervous system is presented as the principal agent of bodily homeostasis. From the philosophic standpoint the volume will be stimulating since, among other things, the author has grasped the importance of the hypothalamus as a primary center of autonomic integration, and he lays emphasis on the fact that all phases of bodily metabolism are ultimately regulated not by the endocrine system in the first instance but by the nervous system.

Although every physiologist is interested in a philosophic unification of the organism and will therefore welcome Professor Gelhorn's presentation, it is not quite clear for whom the book is primarily intended. Medical students will find it valuable as collateral reading, but it will not be an essential textbook since it lacks morphologic detail. It would similarily be helpful for one interested in the surgery of the autonomic system, though scarcely adequate, since there is little reference to practical application and almost none to recent surgical developments relating to the autonomic system. Indeed, it is curious that a book with such an admirable bibliography (1,100 references with full titles) omits reference to the most valuable recent monograph on the autonomic system, namely, the second edition of "The Autonomic Nervous System," by J. C. White and Reginald Smithwick, published in 1941. The subtitle of Gellhorn's book suggests that it may be useful to psychologists and neuropsychiatrists. The chapters on the autonomic basis of emotion can indeed be warmly recommended, as can that on the autonomic system and neuropsychiatry.

One of the principal contributions of Professor Gellhorn and his school has been in the study of the effect of anoxia on the various divisions of the autonomic system, but these papers have nowhere been summarized, and it is a pity that there are only scattered references in the present volume to this timely and important work. Similarly, although the author is eager to establish the primacy of the nervous system in the control of the endocrine glands, details concerning the innervation of these glands, especially the innervation of the pituitary, on which much of his argument hinges, are largely omitted.

Among the virtues of the volume under review is the excellent folding frontispiece prepared by W. R. Ingram, of the University of Iowa, giving a diagram of the hypothalamus and its intracortical connections. A second and conspicuous virtue of the book is that each chapter is systematically summarized at the end. Finally, the bibliography, already mentioned, is not only highly useful but a model of accurate, careful preparation, albeit White and Smithwick are omitted.

Ovarian Tumors. Samuel H. Geist, attending gynecologist, Mount Sinai Hospital; clinical professor of gynecology, College of Physicians and Surgeons, Columbia University. Pp. 527 with 312 illustrations. Price $10.50. New York: Paul B. Hoeber, Inc., Medical Department of Harper & Brothers, 1942.

This book deals with ovarian tumors in the light of the recent advances in the embryology, anatomy and physiology of the ovary. These advances are reviewed in the first three chapters. Then come chapters on general considerations of ovarian tumors; on "benign" epithelial neoplasms of surface origin; proliferating cysts; carcinoma of the ovary; primary parenchymatous epithelial neoplasms of subsurface origin (granulosa cell tumor, theca cell tumor, arrhenoma, dysgerminoma, Brenner tumor); ovular tumors (dermoid, teratoma); stromatogenous (mesoblastic) ovarian tumors; follicular cysts, lutein cysts, endometrial cysts, hematoma, granulomatous lesions, etc.; ovarian tumors in children; parovarian tumors; ovarian tumors in pregnancy; diagnosis and treatment of ovarian tumors. This list not only describes the general contents of the book but illustrates the author's histogenic classification of ovarian tumors. Here "stroma" signifies the musculofibrous framework with vessels and nerves and "parenchyma" the epithelial mass in the body of the ovary, that is to say, the follicular apparatus, the granulosa and theca internal cells, and the embryonal remains in the medulla and rete. The classification as well as the text would have been simplified and improved if "cancer" and "cancerous" had been used in place of "malignant neoplasm" and other such terms, and "malignant." And would it not be preferable to use "choriocarcinoma" or "chorioma" in place of "chorio-epithelioma"? At the end of each chapter is an elaborate bibliography of, as a rule, several pages and covering mainly gynecologic writings in the English and German languages. The book is copiously, not to say overabundantly, provided with photographic illustrations of gross and microscopic appearances, practically all original. The magnification and the staining of the microscopic figures are not given except that in a few cases special methods are mentioned. On page 238 "cell inclusion" is used not to mean, as it usually does, cytoplasmic or nuclear inclusion but inclusion of cells, e. g., adrenal cells within ovarian tissue. And "secondary carcinoma" (page 243) does not mean, as commonly understood, metastatic carcinoma but carcinoma developing in a previously noncarcinomatous tumor. The description of the structure and manifestations of ovarian tumors is excellent. The style is methodical and easily understood, though there is a tendency to use more words and to give more details than necessary. Instructions as to treatment are given in broad outlines as each tumor is described. In the last two chapters the diagnosis and the treatment of ovarian tumors in general are discussed. The chapter on treatment deals mainly with surgical procedures. The experience with radiotherapy does not lead to any definite conclusions. No instructions are given as to methods: "It is essential to utilize adequate radiotherapeutic measures if one is to expect good results," but one is not told what are adequate radiotherapeutic measures. All in all, this is a highly useful, up-to-date, competent book on ovarian tumors.

Books Received

ATLAS OF OVARIAN TUMORS. Gemma Barzilai, M.D., New York. Preface by Fred W. Stewart, M.D., pathologist, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York. Pp. 264, 8½ by 11, with 258 original illustrations, 45 in colors, on 58 plates. Price $10. New York: Grune & Stratton, 1943.

REPORT OF THE SECRETARY OF THE SMITHSONIAN INSTITUTION AND FINANCIAL REPORT OF THE EXECUTIVE COMMITTEE OF THE BOARD OF REGENTS FOR THE YEAR ENDED JUNE 30, 1942. Pp. 112. Price 25 cents. Washington, D. C.: United States Government Printing Office, 1942.

MEDICAL JURISPRUDENCE AND TOXICOLOGY. John Glaister, M.D., D.Sc., fellow of the Royal Faculty of Physicians and Surgeons, Glasgow: Barrister-at-Law of the Inner Temple; regius professor of forensic medicine, University of Glasgow; formerly professor of forensic medicine, University of Egypt, Cairo, and medico-legal consultant to the Egyptian Government. Seventh edition. Pp. 679 with 132 illustrations. Price $8. Baltimore: The Williams & Wilkins Company, 1942,

DISEASES OF THE BREAST, DIAGNOSIS, PATHOLOGY, TREATMENT. Charles F. Geschickter, M.A., M.D., lieutenant commander, Medical Corps, United States Naval Reserve; director of the Francis P. Garvan Cancer Research Laboratory; pathologist, St. Agnes Hospital, Baltimore. With a special section on treatment in collaboration with Murray M. Copeland, M.D., F.A.C.S., instructor in surgery, Johns Hopkins Medical School; visiting surgeon and assistant oncologist, University Hospital, University of Maryland Medical School; visiting oncologist, Baltimore City Hospitals. Pp. 829 with 593 illustrations. Price: $10. Philadelphia: J. B. Lippincott Company, 1943.